Lieke Hofmans

MODULATING MOTIVATION AND COGNITIVE CONTROL

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“No matter. Try again. Fail again. Fail better.”

Samuel Beckett

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CHAPTER 1

General Introduction

It is a Thursday evening and I am preparing a soup for tomorrow. When the soup starts to simmer, I turn on the television to watch my favorite show. All the ins and outs of what is happening to the contestants of the show will be discussed at length during our lunch break at work tomorrow. I then receive a message from a friend, asking how I am doing and how the thesis-writing is going. After some messages back and forth, she starts telling me about her week. I am switching between paying attention to the television show and my friend's story. Suddenly the story becomes more interesting, and I now fully focus on the story, forgetting about the show. In the middle of reading one of her messages, it starts to smell like something is burning, and I quickly run to the stove to save my soup.

Managing our goals, such as preparing a soup, watching television and texting with a friend, is an important aspect of our daily life. At one moment we need to focus on one goal, while at the next moment we need to switch to another, more urgent goal. Sometimes we need to focus on long-term goals, even though other short-term goals seem more appealing.

This thesis is about how we manage our goals, specifically cognitive goals. It is about how well we perform cognitive tasks, but also about how motivated we are to perform well. It is about how we focus on a task, how we prioritize one task over another and how and when we switch between tasks. From now on I will refer to this as cognitive control, a term I will further explain in the next section. Many people with psychiatric or neurological disorders, such as Parkinson's disease, attention-deficit hyperactivity disorder (ADHD), obsessive compulsive disorder or addiction, experience problems with cognitive control. However, healthy people also experience failures of cognitive control from time to time. Some people more than others, and sometimes more on one type of task than on another.

I aim to shed light on the cognitive and neural mechanisms that link motivation and cognitive control, and how this varies across people and tasks. More specifically, in the experiments I present in this thesis I test the effects of pharmacological manipulations, various modulations of how people are rewarded for completing cognitive tasks, and modulations of task context on both cognitive control and the motivation for cognitive control. This first chapter serves to introduce key concepts and give an overview of the literature to provide a rationale for empirical chapters 2 to 6.

Cognitive control and working memory

Cognitive control refers to a set of mechanisms required for adaptively pursuing a (long term) goal, involving preparation and maintenance of rules to bias action and attention

(Egner, 2017; Fuster, 1989; Monsell, 2003). It is an umbrella term that involves linking goals with prior knowledge and context information to direct action. If we go back to the example above, my primary goal might be to prepare a soup for the following day before I go to bed. As I don't want to miss out on the conversation with my colleagues about our favorite show the following day, I have the additional goal to focus on what is happening on the television, all the while keeping up with updates on my friend's story. Managing these goals and knowing when to focus on which goal is guided by prior knowledge. For example, I know I need to go back to the stove when I hear it boiling to lower the heat and bring it back to a simmer. I also know that my friend usually sends multiple short messages rather than one long one. So I know that I do not need to read each message as it comes in, but I can wait until she has sent at least five messages before I turn my attention away from the television. However, this all changes when my friend's story suddenly becomes more interesting. This change of context shifts my priorities. The story becomes my primary goal, while I totally forget to pay attention to the television and my soup. Only when it starts to smell like something is burning, my attention is brought back to the soup.

What are the mechanisms that allow us to use prior knowledge and contexts to update our goals and guide our behavior? Information about the current context must be actively maintained to decide what prior knowledge, out of our vast life experience, is relevant and which goals need to be prioritized over others. Our working memory is essential to maintain that information in mind. Our working memory serves to maintain small amounts of information for a short period of time, manipulate it and act upon it. It is widely accepted that the prefrontal cortex is important for maintaining task or contextual information in working memory. Multiple studies have shown enhanced activity or firing rates of neurons in the prefrontal cortex during various phases of working memory tasks, including the encoding of stimuli, the delay period and the retrieval of stimuli (Cohen et al., 1994; Fuster & Alexander, 1971; Goldman-Rakic, 1995; Miller et al., 1996). Importantly, the prefrontal cortex does not act in isolation during these tasks. Its activation is associated with activation in other brain regions, including temporal and parietal regions, suggesting that connectivity between these regions enhances sensory stimulus information or motor plans (Braver et al., 1997; Curtis & D'Esposito, 2003; J. B. Rowe et al., 2000).

Our working memory capacity is limited. We cannot hold in memory all the input around us, and not all input is relevant to a current task. Thus, we need some kind of a selection process to decide what information should enter our working memory and what information should be shut out. Moreover, this process needs to be dynamic, because what is relevant at one moment, might be less relevant at the next moment. I considered my soup not that relevant when my friend's story became very interesting,

but it became very relevant when I started to smell the burning smell. This means that we constantly need to balance the extent to which we focus on one task (cognitive stability) versus the extent to which we flexibly switch between tasks (cognitive flexibility), depending on ever changing inputs and goals. How does the brain decide when to focus and when to allow new input and demands to enter our working memory?

The process by which stimuli are granted access to our working memory is called working memory gating (Braver & Cohen, 2000). When no new inputs are gated into working memory, our task representations are very stable, we can resist distractions and can strongly focus on the task at hand. When the gates open to new inputs, new context or task information enters our working memory and we can shift our goals and switch tasks. Thus, we need control over which information enters working memory. The system that is considered to control the input to working memory is the cortico-basal ganglia system (Frank et al., 2001; Hazy et al., 2007)(Box 1). The prefrontal cortex is innervated by a structure deep in the brain called the thalamus, which is considered the relay-station of the brain, relaying sensory input to the cortex for further processing. However, the thalamus, and thereby the connection with the prefrontal cortex, is usually suppressed by other neurons. When this suppression is removed, information can be gated into the prefrontal cortex and our working memory. There are two main basal ganglia pathways influencing this gating system. Activation of the first one reduces the suppression of the thalamus, resulting in an increased connection between the thalamus and the prefrontal cortex. Because this allows information to access the prefrontal cortex, this pathway is often referred to as the direct Go pathway. The second basal ganglia pathway strengthens the suppression of the thalamus, resulting in reduced information flow between the thalamus and the prefrontal cortex, thus closing the gate to working memory. This pathway is therefore often referred to as the indirect NoGo pathway. These Go and NoGo pathways receive input from various brain regions to decide whether the gates to working memory should open or close, including input from sensory structures and feedback from the prefrontal cortex. Importantly, there are many parallel connections in the cortico-basal ganglia system. This way, specific input can be gated while other input is suppressed. When the system suppresses most input, activity in the prefrontal cortex promotes cognitive stability, or the maintenance of current task information. Conversely, when the system allows input to enter working memory, cognitive flexibility is promoted by new information updating task rules or goals. In the next section, I will go deeper into the neurochemistry of these processes and ways in which we could modulate them using medication.

Box 1 | Cortico-basal ganglia system

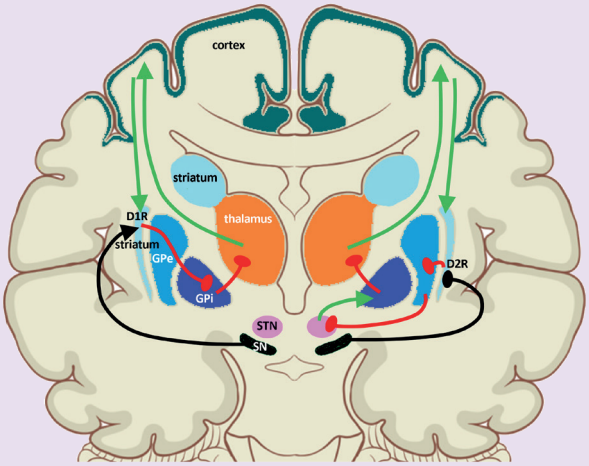

FIGURE 1.1 | Depiction of the cortico-basal ganglia system. Activating connections are depicted in green, inhibiting connections are depicted in red, and dopaminergic connections are depicted in black. NB: The direct (left) and indirect (right) pathway can be found in both hemispheres, but are here presented lateralized for illustrative purposes.

The cortico-basal ganglia system is important for allowing new information to enter the prefrontal cortex and working memory. The thalamus relays information from other brain regions to the prefrontal cortex. However, the thalamus is inhibited by the internal globus pallidus (GPi).

The Go pathway releases this inhibition: A structure called the striatum inhibits the internal globus pallidus. This is termed disinhibition, resulting in activation of the thalamus. The NoGo pathway strengthens the inhibition of the thalamus by the internal globus pallidus: The striatum inhibits the external globus pallidus (GPe), which in turn inhibits the subthalamic nucleus (STN), which innervates the internal globus pallidus. This results in activation of the internal globus pallidus, and thus stronger inhibition of the thalamus. This means that the Go pathway facilitates information to enter the prefrontal cortex, promoting cognitive flexibility, whereas the NoGo pathway prevents information from entering the prefrontal cortex, promoting cognitive stability.

The Go and NoGo pathways receive information from different brain regions, including feedback from the prefrontal cortex and dopaminergic input from the substantia nigra pars compacta (SN). Dopamine increases activity of the Go pathway via D1 receptors (D1R), while it inhibits activity of the NoGo pathway via D2 receptors (D2R). The net input to the Go and NoGo pathway determines which pathway wins the competition, and whether information flows between the thalamus and the prefrontal cortex.

The role of dopamine in cognitive control

The pathways of the neurotransmitter dopamine have their starting point in the midbrain, specifically in the substantia nigra and the ventral tegmental area (Figure 1.2). Dopaminergic connections run from the midbrain to both the prefrontal cortex and the basal ganglia and are therefore well suited to play a role in cognitive control. Drugs that alter dopamine transmission are used as first-line treatment for disorders that are accompanied by deficits in cognitive control, such as methylphenidate to treat ADHD (Arnsten & Plizska, 2011; Prince, 2008) and levodopa to treat Parkinson's disease (Connolly & Lang, 2014). Dopaminergic drugs such as methylphenidate are also commonly used as smart drugs by healthy people to enhance cognition (Greely et al., 2008; Husain & Mehta, 2011; Schelle et al., 2015). However, it is still unknown how exactly these drugs work. For example, do these drugs enhance stability, flexibility, or perhaps both?

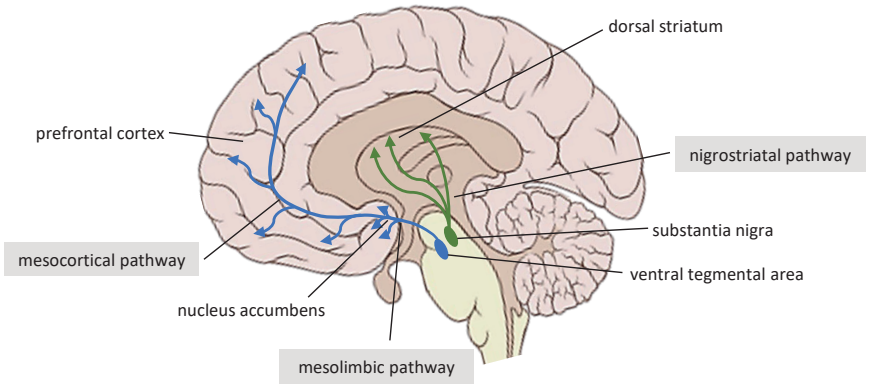

FIGURE 1.2 | Major dopamine projections. The mesocortical pathway originates in the ventral tegmental area and projects to the prefrontal cortex. The mesolimbic pathway originates in the ventral tegmental area and primarily projects to mesolimbic regions including the nucleus accumbens. The nigrostriatal pathway originates in the substantia nigra and primarily projects to the dorsal striatum (caudate nucleus and putamen).

Dopamine has long been implicated in cognitive control and prefrontal cortex functioning (Brozoski et al., 1979; Goldman-Rakic, 1995; Robbins, 2000; Robbins & Arnsten, 2009; Servan-Schreiber et al., 1990). Using chemicals, researchers depleted dopamine in the prefrontal cortex of monkeys, which led to impairments in working memory almost to the same degree as completely removing the prefrontal cortex (Brozoski et al., 1979). Moreover, optimal levels of dopamine in the prefrontal cortex of monkeys have been found to suppress processing of non-relevant information during a working memory task, increasing the signal to noise ratio of relevant information (Vijayraghavan et al., 2007). Of note here is that too much dopamine led

to the additional suppression of relevant information, resulting in poorer performance. Although it is still an open question how exactly, these studies suggest that dopamine in the prefrontal cortex is important for increasing the signal-to-noise ratio of information, thereby enhancing cognitive stability (Durstewitz & Seamans, 2008).

In addition to its role in prefrontal functioning, dopamine has also been implicated in striatal functioning. Dopaminergic connections from the midbrain to the striatum affect the Go and NoGo pathways in the basal ganglia, which are part of the gating system of working memory. Striatal cells belonging to the Go pathway receive dopaminergic signals via a type of dopamine receptors called D1 receptors, which activate the pathway, whereas cells belonging to the NoGo pathway receive dopaminergic signals via D2 receptors, which inhibit the pathway (Box 1). This results in an overall Go bias and thereby a greater readiness for information to enter the prefrontal cortex and working memory (Frank et al., 2001; Hazy et al., 2007). Thus, striatal dopamine enhances cognitive flexibility.

Is sum, dopamine can have different effects depending on the neural region it modulates: Dopamine in the prefrontal cortex is expected to enhance cognitive stability whereas dopamine in the striatum is expected to enhance cognitive flexibility (Cools, 2019; Cools & D'Esposito, 2011). Indeed, dopamine depletion in the prefrontal cortex of marmosets caused increased distractibility by task-irrelevant stimuli on a task testing attentional performance, whereas dopamine depletion in the dorsal striatum decreased distractibility (Crofts et al., 2001). For obvious reasons, such direct manipulations of dopamine transmission in specific brain areas are not allowed in human participants. In humans, dopaminergic drugs are given systemically, for example through intravenous administration or in the form of a pill or capsule. After crossing the blood-brain barrier, these drugs can potentially influence multiple brain regions, restricting drawing firm conclusions about local specificity. Thus, even though dopaminergic drugs such as methylphenidate are often used, we do not yet fully understand how they work. What are their effects on stability versus flexibility? Moreover, do they affect cognitive control directly or indirectly? As I will lay out below, cognitive control is not just about ability, but is also affected by our motivation to exert cognitive control. For example, cognitive and attentional deficits often associated with ADHD may be related to effort and motivational deficits, such as altered reward sensitivity, in agreement with a cognitive-energetic model of ADHD (Sergeant, 2000, 2005; Volkow et al., 2011). Other questions are therefore whether dopaminergic drugs also alter the willingness, rather than the ability, to exert cognitive tasks and whether and how they modulate reward sensitivity? In this thesis, I aim to advance our understanding on the role of dopamine in linking motivation and cognitive control. In the following sections, I will discuss the interplay between motivation and cognitive control, followed by the role of dopamine

herein. Throughout the text, I will refer to specific chapters examining certain sub-questions, finishing with an outline of this thesis.

Motivation and cost-benefit analyses

In the previous sections I explained how cognitive control depends on working memory processes, and how the cortico-basal ganglia gating system allows information to enter our working memory. I will now discuss how this gating system is affected by motivation. Going back to our example, as soon as my friend's story turned interesting, the context in which I was watching television, reading my messages, and preparing my soup changed. Reading messages became more *valuable* to me. This led me to focus on my messages, while suppressing input from the television or the boiling soup. When I started to smell something burning, the context changed yet again. The soup became more valuable. Or rather, the potential cost of staying focused on my messages and not attending to my soup became too high, upon which I decided to run to my soup. Thus, cognitive control and working memory gating can be framed as involving a decision about the costs and benefits associated with different tasks (Cools, 2016).

The benefit of a task can comprise a promised reward upon successful completion of a task. This could be the motivation of a participant of one of my studies, whom I pay for their participation. It can also be that someone decides to participate in a study because they are curious to try out methylphenidate (also known by its tradename Ritalin®), which they were asked to do in one of my experiments (**Chapter 2**). Someone might also be genuinely interested in a task, such as participating in a scientific study, or enjoy the process, such as when I try to solve a crossword puzzle.

The cost of a task can be associated with the mental effort you need to engage in to complete a task, which is often experienced as aversive (Kool & Botvinick, 2014; Massar et al., 2016; Westbrook et al., 2013). Although it is still an open question what exactly constitutes this aversiveness or cost of engaging in cognitive control, it has been suggested that intrinsic costs such as task demands, response conflict, error-likelihood and risk play a role (Apps et al., 2015; Cavanagh et al., 2014; Dunn et al., 2019; Kool & Botvinick, 2013). Another source of cost is that one can only deploy cognitive resources for a limited number of simultaneous tasks. This means that by focusing on a certain task, you forego benefits you could have obtained by spending the same amount of time or resources on an alternative task. The notion of foregone benefits or 'opportunity costs' has been important in relation to foraging (Charnov, 1976; Kolling et al., 2012). When an animal is foraging in a certain food patch, it cannot simultaneously forage in another potentially valuable patch. The Marginal Value Theorem describes that an

animal should leave the current patch to explore other patches as soon as the reward rate, or the rate at which food is encountered, falls below the average reward rate of alternative patches (Charnov, 1976). This theory has been corroborated by research in human participants, showing that people indeed more readily switch to alternative options when either the average reward rate of these alternative options is higher or when the current option becomes less valuable (Constantino & Daw, 2015; Kolling et al., 2012; Le Heron et al., 2020).

Insights from the foraging literature have been leveraged for our understanding of cost-benefit decision-making about cognitive effort. By using cognitive resources for one task, one foregoes the opportunity to use these resources for other cognitive tasks. It has been argued that the subjective feeling of effort during a task is the felt consequence of these opportunity costs, such that we experience a task as more effortful when it carries higher opportunity costs (Boureau et al., 2015; Kurzban et al., 2013). This higher opportunity cost or stronger feeling of effort should then lead people to quit focusing on the current task and switch to an alternative, more valuable task. However, calculating the opportunity costs of a task is usually not straightforward: You have to take into account all other possible tasks you could have been doing, which is quite a large number of alternatives in our complex world. This computation itself would demand a lot of cognitive resources and would thus be very costly. Therefore, a simpler way to approximate these costs is to keep track of the long-term average reward rate of rewards received over time (Boureau et al., 2015; Niv et al., 2007). Over time, we encounter tasks that are highly rewarding or less rewarding. When we keep track of the average value of the rewards we have received over time for completing these tasks, we can compare the reward we expect to receive for the current task with this average value. If the current task has greater value than the long-term average, it is worth focusing on that task. Otherwise, if the current task's value falls below the average, we should abandon the task and explore alternative tasks with potentially higher values (Charnov, 1976).

Thus, to decide whether and how strongly to focus on a task or to update our working memory and flexibly explore other options, we need to continuously engage in cost-benefit analyses to compute the expected net value of control (Shenhav et al., 2013, 2017). Based on these computed values, we select tasks or cognitive strategies that maximize our expected reward rate.

So far, I have discussed that cognitive control and working memory rely on the prefrontal cortex and basal ganglia for the maintenance and updating of information, and that motivation and rewards play a role in deciding which information is valuable enough to attend to. In the next section, I will review how motivation modulates cognitive control at the neural level.

The role of dopamine in linking motivation and cognitive control

In addition to its role in cognitive control directly, dopamine has also been implicated in motivation and reward processing. Using a paradigm where monkeys received a reward in the form of a juice after hearing a tone, it was found that midbrain dopamine cells got activated upon receiving the reward (Schultz, 1997). Later in the experiment, when the animals had learned the association between the tone and the reward, the midbrain dopamine cells did not respond to the reward anymore, but rather to the tone predicting the reward. Interestingly, activity in the dopamine cells was suppressed when the tone sounded, but no reward arrived. This has been interpreted as a reward prediction error signal, which is the difference between the reward received and the reward predicted (Montague et al., 1996). Early in the experiment, the reward was unexpected, leading to a positive prediction error and increased dopamine activity. Later, the monkey expected to receive a reward after hearing the tone, so there was no difference between the expected and the received reward and no change in dopamine activity. When the monkey did not receive the expected reward after hearing the tone, this resulted in a negative prediction error and a dip in dopamine activity in the midbrain. In the subsections below I will review the role of dopamine in linking motivation and cognitive control from two different perspectives. First, how does dopamine affect our choices about exerting cognitive control? This will also be the topic of the first experimental chapter, **chapter 2**. Second, how does dopamine interact with reward effects on cognitive control? **Chapters 3-6** ultimately aim to investigate this latter question, with a special emphasis on the balance between stable and flexible cognitive control.

Dopamine and cost-benefit decision-making

As we have seen above, cognitive performance is governed by cost-benefit analyses. How then, does dopamine affect the choices we make about exerting cognitive control? In the animal literature it has repeatedly been shown that dopaminergic manipulations, such as neuronal lesions or pharmacological interventions, affected the willingness to choose a more effortful option (such as climbing a barrier) for more reward versus a less effortful option (without a barrier) for less reward. Decreasing dopamine made the animals choose the high effort/high reward option less often, which could not be attributed to motor deficiencies (Salamone et al., 2009). Similar findings have been observed in humans, with the indirect dopamine agonist amphetamine increasing participant's willingness to exert physical effort (button pressing) for reward (Wardle et al., 2011). Moreover, participants with Parkinson's disease, characterized by striatal dopamine depletion, chose to exert less physical effort (squeezing a handgrip) in return

for reward than healthy control participants. This motivational deficit was eliminated when they took their medication, restoring dopamine levels (Chong et al., 2015; Le Bouc et al., 2016). These findings were replicated using a cognitive attentional task, rather than a physical task, showing that Parkinson's patients off their dopaminergic medication were less willing to opt for a high effort/high reward option than healthy control participants, but this was ameliorated when they were on their medication (Mcguigan et al., 2019).

Thus, dopamine appears to increase the balance of benefits over cost. This is captured by a neurocomputational framework of striatal dopamine: Activity in the Go pathway is argued to signal the benefits of an action, whereas activity in the NoGo pathway in argued to signal the costs of an action. Dopamine emphasizes processing in the Go pathway through D1 receptors and suppresses processing in the NoGo pathway through D2 receptors (Box 1). Striatal dopamine therefore increases the sensitivity to differences in benefits between options and decreases the sensitivity to differences in costs between options, resulting in more high effort/high reward choices (Collins & Frank, 2014). Later experimental and computational work has corroborated this by showing that reward cues enhanced both speed and accuracy on a task requiring rapid saccades to a target. This effect of reward cues was smaller in patients with Parkinson's diseases, which could computationally be accounted for by a higher cost for increasing the signal-to-noise ratio, or precision, in patients, being suggestive of an important role for dopamine in the reduction of effort costs (Manohar et al., 2015).

Open questions are whether and how dopaminergic medication plays a role in the valuation of cognitive control or in decision-making about whether to exert control in healthy, human participants. Does dopamine indeed increase sensitivity to the benefits and decrease sensitivity to the costs, thereby biasing people to engage in cognitive effort? I will address this in **chapter 2**, where I examine the effect of the dopamine transporter blocker methylphenidate (Box 2) on decision-making about engaging in cognitive effort in healthy participants. This is societally relevant, as methylphenidate is not only clinically prescribed to patients with ADHD to enhance cognitive control but also widely used as a smart drug by the healthy population.

Dopamine, reward and the stability-flexibility balance

Midbrain dopamine cells, which are activated in response to reward, project to both the prefrontal cortex and the striatum. As we have seen, dopamine might have differential effects, arguably depending on its locus of control. This poses the question what will happen to the stability-flexibility balance when we encounter a reward or are highly motivated? Will rewards increase stability or will they increase flexibility?

At first sight, and perhaps also in line with intuition, incentive motivation (motivation activated by external reward cues, such as a promised monetary reward upon successful completion of task) generally improves focus and cognitive control (Pessoa, 2017). For example, participants performed faster (and as accurate) on a working memory task when they could earn a reward, compared with when they could not earn a reward (Krawczyk et al., 2007). At the neural level, high reward trials enhanced activation in task relevant brain areas in the prefrontal cortex and in brain regions representing stimuli that should be attended to, and reduced activation in brain regions representing stimuli that should be ignored, indicating increased attention and distractor resistance. Similar results were found in a study testing response conflict, where participants had to respond whether a picture depicted a house or another type of building, while ignoring an overlaid word "house" or "bldng" which could either be congruent or incongruent with the picture (Padmala & Pessoa, 2011). Participants exhibited reduced conflict at the behavioral level, indicated by faster response times, and stronger neural activation of frontoparietal attentional networks on reward versus no-reward trials. Interestingly, however, they also found stronger coupling between striatal regions and frontoparietal regions during the reward condition, suggesting that increased focus is not a result of merely increased frontal activity. Correspondingly, a study directly comparing flexible updating and distractor resistance found increased activity in and connectivity between the ventral striatum and prefrontal cortex on trials in which participants received a performance-independent reward compared with a loss, which was associated with better distractor resistance and poorer updating at the behavioral level (Fallon & Cools, 2014). In a later study, the authors aimed to assess the effect of de dopamine transporter blocker methylphenidate on these reward-related neural effects (Fallon et al., 2017). They found that, at the behavioral level, methylphenidate increased distractor resistance at the expense of updating. At the neural level, methylphenidate increased activity in the prefrontal cortex during trials requiring distractor resistance while reducing them during trials requiring updating. Methylphenidate also increased activity in the striatum, independent of trial-type. This task-general increase in striatal activity was hypothesized to be a prerequisite for the task-specific effect in the prefrontal cortex, although connectivity between the areas was not analyzed. Importantly, though, these methylphenidate-induced effects did not interact with the effect of reward, neither on the behavioral nor on the neural level. These studies indicate that motivation improves attention and focus through increased connectivity between striatal and prefrontal areas.

Results more in line with motivation improving flexibility have also been found (Aarts et al., 2010; van Holstein et al., 2011). For example, incentive motivation improved task switching, indicative of improved flexibility, in people with a genetic polymorphism associated with high striatal dopamine levels (Aarts et al., 2010), suggesting that

incentive motivation and dopamine transmission in the striatum have an interactive effect on cognitive control. At the behavioral level, other researchers have found that inducing performance-independent positive affect, for example by having participants listen to happy or pleasant music, increased susceptibility to distracting information (G. Rowe et al., 2007) and reduced focus after a trial with conflicting information (van Steenbergen et al., 2010). Similarly, simply observing positive affective pictures promoted cognitive flexibility, while increasing distractibility in a set-switching paradigm (Dreisbach & Goschke, 2004) and reducing maintenance of information in a Continuous Performance Test (Dreisbach, 2006).

These contrasting results illustrate that it is still unclear whether rewards primarily act on the prefrontal cortex to enhance cognitive stability, or on the striatum to enhance cognitive flexibility (Aarts et al., 2011; Cools & Robbins, 2004), or perhaps alter the connectivity between striatal and prefrontal regions. Additionally, it is still unknown how dopaminergic medication interacts with the effect of reward, both at the behavioral and the neural level. In **chapters 3-5** I address these open questions by aiming to establish a paradigm to assess reward effects on cognitive stability versus flexibility, with the ultimate goal to investigate the effect of dopamine on these reward effects. In these chapters I will also address other open issues regarding reward effects. For example, it is unclear how task contexts influence the effect of rewards on the stability/flexibility balance (Dreisbach & Fröber, 2019; Goschke & Bolte, 2014). The prospect of a reward has been argued to increase a form of meta-control, which facilitates preparation (Chiew & Braver, 2016). This increased meta-control would then enhance cognitive stability in tasks requiring maintenance and distractor resistance, but can also enhance flexibility when tasks require updating (Goschke & Bolte, 2014). I will address this potential interaction between task requirements and reward in **chapter 3** of this thesis by investigating whether incentive motivation indeed improves meta-control over the stability/flexibility balance. Yet another open issue is that performance-dependent and performance-independent rewards seem to have different effects. Notably, Braem et al. found different effects of performance-dependent versus performance-independent rewards on the stability/flexibility balance, with performance-dependent rewards improving flexibility over stability but performance-independent rewards having the reverse effect (Braem et al., 2013). Therefore, I will specifically focus on performance-independent rewards in **chapter 4**. Moreover, individual differences in baseline dopamine levels might play a role in reward-related effects, as I will discuss in more detail below. In **chapter 5** I will assess whether effects of incentive motivation on the stability/flexibility balance indeed depend on individual differences related to dopamine transmission.

Individual differences in the effects of reward and dopamine manipulations

So far, I have reviewed the effects of rewards and dopamine manipulations on cognitive control and decision-making about exerting cognitive control across individuals. However, there is large individual variation, with the effects depending on baseline conditions. For example, administration of amphetamine to rodents decreased cognitive task avoidance in 'slackers', while increasing it in 'workers' (Cocker et al., 2012). By analogy, the effects of the stimulant methylphenidate on cognitive demand avoidance in young healthy human volunteers depended on trait impulsivity, with high impulsive participants becoming more avoidant of cognitive control than low impulsive participants (Froböse et al., 2018). Such contrasting effects on cognitive task avoidance are reminiscent of the variable effects of methylphenidate (and dopamine receptor agonists, such as bromocriptine) on task performance, with greater beneficial effects in participants with higher trait impulsivity (Clatworthy et al., 2009; Cools et al., 2007). Effects of dopamine medication on cognitive task performance have also been shown to depend on working memory capacity under baseline conditions (Kimberg et al., 1997; Kimberg & D'Esposito, 2003; Mehta et al., 2000). These individual variations in drug responses are hypothesized to reflect variation in baseline dopamine levels (Cools & D'Esposito, 2011), as trait impulsivity is associated with low (presynaptic) dopamine receptor availability and high striatal dopamine release (Buckholtz et al, 2010; Lee et al, 2009; Kim et al, 2014; Reeves et al, 2012), and working memory capacity is associated with dopamine synthesis capacity (Cools et al, 2008; Landau et al, 2009). Prior work indeed suggests that individual variation in the effects of dopamine medication and reward on cognitive control depends on baseline dopamine-related functioning, such as dopamine cell loss in Parkinson's disease (Aarts et al., 2012), dopamine transporter genotype (Aarts et al., 2010, 2015; van Holstein et al., 2011), dopamine receptor availability (Samanez-Larkin & Buckholtz, 2013) and dopamine synthesis capacity (Aarts et al., 2014; Cools et al., 2009). This principle of baseline-dependency postulates that increases in dopamine, in response to dopamine medication or reward, have positive effects when baseline dopamine levels are low by shifting dopamine levels from suboptimal to optimal, but even negative effects when baseline levels are already high by shifting dopamine levels from optimal to supra-optimal (Cools & D'Esposito, 2011). These negative effects are conceived to occur because supra-optimal dopamine levels in the prefrontal cortex drive noise reduction to the point where not only irrelevant but also relevant information is suppressed. Supra-optimal dopamine levels in the striatum would drive the updating of information to the point where it is no longer selective. However, there is also prior evidence for the opposite direction of baseline-dependency, with greater effects of dopamine enhancing drugs in high baseline-dopamine individuals (or individuals scoring high on

dopamine-proxy measures)(Samanez-Larkin & Buckholtz, 2013; Swart et al., 2017; van Der Schaaf et al., 2013; Volkow et al., 2002).

Thus, variation in the effects of rewards and dopamine manipulation might be explained by individual differences in baseline dopamine conditions. I will delve into these aspects in several chapters: In **chapter 1** I assess effects of dopaminergic drugs on cognitive motivation as a function of an individual's baseline dopamine synthesis capacity and in **chapters 5 and 6** I investigate the effects of incentive motivation on cognitive control as a function of trait impulsivity and as a function of baseline dopamine synthesis capacity, respectively.

Summary and thesis outline

In the literature review above, we have seen that our cognitive control system involves linking goals with prior knowledge and task context. I have reviewed that the updating and maintenance of new information in working memory are important facets of cognitive control. I have discussed that cognitive control is not just about the ability to execute tasks, but also about willingness, such that we prioritize some tasks over others based on a cost-benefit analysis. I have also reviewed that the neuromodulator dopamine plays an important role in both the updating and the maintenance of information, as well as in the motivation for cognitive control, but that different studies have provided contrasting results as to the direction and the strength of these effects. Lastly, the effects of dopamine and rewards are hypothesized to depend on both baseline dopamine levels and task demands.

The aim of this thesis is to provide a deeper understanding of the role of dopamine in the motivation for cognitive control. I approach this issue from two different angles: i) By assessing the role of dopamine in decision-making about whether to exert cognitive effort (**chapter 2**) and ii) by assessing the effect of reward and incentive motivation on cognitive performance and its modulation by dopamine (**chapters 3-6**).

In **chapter 2** I assessed whether the stimulant methylphenidate, often used to enhance cognitive performance in both clinical and healthy populations, also affects people's valuation of cognitive effort. Specifically, I assessed the effect on their motivation for completing a cognitive working memory task versus leisure and whether the extent of this effect depends on baseline dopamine synthesis capacity. To that end, fifty healthy participants were tested on methylphenidate and placebo. To investigate the hypothesis that methylphenidate selectively affects dopaminergic signaling (rather than noradrenergic signaling; Box 2), participants were also tested on the selective

dopamine D2-receptor agent sulpiride. Furthermore, they underwent a PET scan using the radiotracer [^{18}F]DOPA, a radioactive precursor of dopamine, to quantify striatal dopamine synthesis capacity. The findings indicate that methylphenidate boosts choices of cognitive effort over leisure across the group, and that this effect is stronger in participants with more striatal dopamine synthesis capacity. The effects of sulpiride did not reach significance.

After assessing the effect of dopamine medication on the *valuation* of a cognitive task, I then focus on developing a paradigm with the goal to assess the role of dopamine in the *incentivization* of stable versus flexible cognitive control in the subsequent chapters. In **chapter 3** I assessed whether contextual aspects modulate incentive effects on the stability/flexibility balance. I tested whether reward cues improve strategic meta-control using a working memory paradigm that distinguishes between two different trial-types, one requiring cognitive stability and the other requiring flexibility. I manipulated the extent to which participants could exert strategic meta-control by varying the frequency of one trial-type over the other, allowing participants to prepare for the high-frequent trial type. I expected participants to be better prepared for demands for flexibility or stability when either is, respectively, more frequent, and that higher reward cues strengthen this effect.

As the results in chapter 3 were inconclusive, I examined the effect of a different reward manipulation in **chapter 4**. In contrast with the reward manipulation in chapter 3, where rewards were contingent on how well the participant performed the task, rewards in chapter 4 were independent of performance. I tested whether highly rewarding environments are associated with improved cognitive flexibility but reduced cognitive stability. I predicted that high non-contingent reward not only improves cognitive flexibility in terms of performance, but also reduces the subjective cost of cognitive flexibility versus stability, measured with a subsequent cognitive effort discounting procedure.

As chapters 3 and 4 did not yield significant effects of our reward manipulations, I wondered whether any effects could be exposed when taking into account individual differences in **chapter 5**. Specifically, I asked whether reward cues enhance performance on a task requiring cognitive flexibility at the expense of performance on a task requiring cognitive stability, and whether this effect depends on trait impulsivity, a supposed proxy of dopamine signaling. Again, this provided inconclusive results.

The inconclusive results regarding the effects of reward on working memory performance in chapters 3 to 5 could potentially be due to the working memory paradigm being insensitive to reward manipulations, rather than reward having no

effect on cognitive control in general. Moreover, individual differences in dopamine transmission could play a role, which is not accounted for in chapters 3 and 4, and only indirectly assessed using a proxy-measure in chapter 5. Therefore, I asked whether I could recover previously found effects of incentive motivation on cognitive control as a function of a direct measure of dopamine levels, using an established paradigm in **chapter 6**. I aimed to replicate earlier findings by Aarts and colleagues (2014), who demonstrated, in 14 individuals, that the effect of reward cues depended on individual differences in striatal dopamine synthesis capacity, measured with [^{18}F]FMT-PET: High reward cues improved cognitive control in low-dopamine individuals, while impairing it in high-dopamine individuals. These findings were attributed to an overdosing of already high baseline dopamine levels by further dopamine increases elicited by reward cues. In **chapter 6**, I assessed this same effect in 44 participants, who had previously undergone an [^{18}F]DOPA-PET scan (chapter 2) to quantify dopamine synthesis capacity. However, I show that the cognitive effects of a high reward cue do not depend on dopamine synthesis capacity in this new study.

I summarize the main findings of those experiments in **chapter 7** and discuss them in light of the literature, while also discussing limitations and implications of the studies.

Box 2 | Dopamine transmission

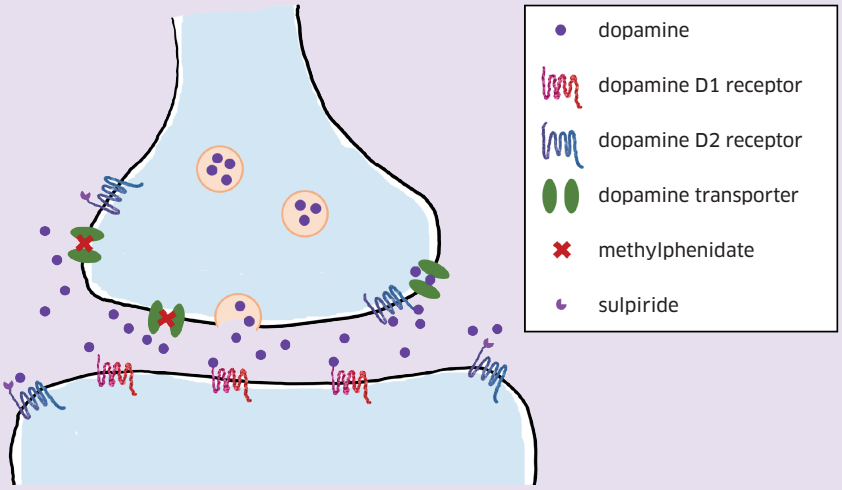

FIGURE 1.3 | Depiction of dopamine transmission.

Dopamine is released from dopamine vesicles in the presynaptic neuron (upper neuron) into the synaptic cleft. Dopamine can then stimulate D1 receptors on the postsynaptic neuron (lower neuron), facilitating activation of the postsynaptic neuron, or D2 receptors, inhibiting the activation of the postsynaptic neuron. Dopamine can also stimulate D2 receptors on the presynaptic neuron, providing negative feedback to inhibit dopamine transmission. Dopamine action can be terminated by reuptake into the presynaptic neuron by dopamine transporters.

In chapter 2, we used methylphenidate and sulpiride to alter dopamine transmission. Methylphenidate is a dopamine transporter blocker, blocking the reuptake of dopamine and thereby increasing dopamine transmission.

However, this transporter is also responsible for the reuptake of another neurotransmitter, noradrenaline. To test whether the effects of methylphenidate were dopaminergic rather than noradrenergic, we also looked at the effect of sulpiride, which has a selective action on dopamine transmission. Sulpiride is a D2 receptor antagonist, meaning that it blocks the D2 receptor, inhibiting the action of dopamine. When sulpiride binds postsynaptically, it blocks the activation of the postsynaptic D2 receptors. However, when binding to presynaptic D2 receptors, it increases dopamine transmission, thereby indirectly activating the D2 receptors at the postsynaptic neuron.

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CHAPTER 2

Methylphenidate boosts choices of mental labor over leisure depending on striatal dopamine synthesis capacity

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Abstract

The cognitive enhancing effects of methylphenidate are well established, but the mechanisms remain unclear. We recently demonstrated that methylphenidate boosts cognitive motivation by enhancing the weight on the benefits of a cognitive task in a manner that depended on striatal dopamine. Here we considered the complementary hypothesis that methylphenidate might also act by changing the weight on the opportunity cost of a cognitive task, that is, the cost of foregoing alternative opportunity. To this end, fifty healthy participants (25 women) completed a novel cognitive effort discounting task that required choices between task and leisure. They were tested on methylphenidate, placebo as well as the selective D2-receptor agent sulpiride, the latter to strengthen inference about dopamine receptor selectivity of methylphenidate's effects. Furthermore, they also underwent an [^{18}F] DOPA PET scan to quantify striatal dopamine synthesis capacity. Methylphenidate boosted choices of cognitive effort over leisure across the group, and this effect was greatest in participants with more striatal dopamine synthesis capacity. The effects of sulpiride did not reach significance. This study strengthens the motivational account of methylphenidate's effects on cognition and suggests that methylphenidate reduces the cost of mental labor by increasing striatal dopamine.

Introduction

The brain catecholamines have long been implicated in a wide range of cognitive functions, including working memory and cognitive control (Arnsten et al., 2015; Cools & D'Esposito, 2011; Goldman-Rakic, 1997). Drugs altering catecholamine transmission are first-line treatment for disorders accompanied by deficits in working memory and cognitive control, such as attention deficit/ hyperactivity disorder (ADHD) (Arnsten & Plizska, 2011; Prince, 2008) and are commonly used for cognitive enhancement in healthy people (Greely et al., 2008; Husain & Mehta, 2011; Schelle et al., 2015). Various studies have demonstrated that acute administration of psychostimulants, like the dopamine and noradrenaline transporter blocker methylphenidate, enhances working memory and cognitive control and decreases feelings of fatigue in healthy individuals (Elliott et al., 1997; Fallon et al., 2017; Repantis et al., 2010; Roehrs et al., 1999; Rogers et al., 1999; Samanez-Larkin & Buckholtz, 2013; Spronk et al., 2013; Ter Huurne et al., 2015).

Such cognitive effects of catecholaminergic drugs have been most commonly attributed to a modulation of the ability to implement cognitive control, often associated with the prefrontal cortex (Arnsten et al., 2015). However, recent progress suggests that cognitive control might also be altered by changing motivation, that is the willingness to engage with a cognitive task, rather than ability alone (Manohar et al., 2015; Mcguigan et al., 2019). Specifically, we have posited that the cognitive enhancing effects of drugs like methylphenidate, which act by blocking the dopamine and noradrenaline transporters, reflect changes in cost/benefit-based decision making about cognitive control, elicited by striatal dopamine (Cools, 2015; Froböse & Cools, 2018). While prior evidence, for example from medication withdrawal studies in Parkinson's disease, generally concurred with this hypothesis (Clark et al., 1986; Froböse et al., 2018; Mcguigan et al., 2019; Wardle et al., 2011) (but see (Hosking et al., 2015)), there was, until recently, no direct evidence for a specific role for dopamine in the striatum. To definitively test this role for striatal dopamine in cognitive motivation, we set up two separate cognitive effort discounting experiments in the context of a large pharmacological PET study with 100 healthy volunteers. In this study we directly quantified striatal dopamine synthesis capacity with PET, while also measuring effects of methylphenidate and sulpiride. In both experiments, participants completed a working memory task prior to drug administration and a cognitive effort discounting task after drug administration, allowing us to isolate drug effects on motivation in a manner that was not confounded by drug effects on performance. In a separate session, participants underwent an [^{18}F] DOPA PET scan to quantify dopamine synthesis capacity. Uptake of the radiotracer [^{18}F]DOPA indexes the degree to which dopamine is synthesized in (the terminals of) midbrain dopamine neurons, providing a relatively stable trait index of dopamine

transmission that is less sensitive to state-dependent changes in dopamine levels (Egerton et al., 2010) (but see (Schabram et al., 2014)) than other dopamine PET tracers such as [11C]raclopride or [^{18}F]fallypride, which reflect D2/3-receptor availability. To substantiate the hypothesis that the effects of the non-specific catecholamine enhancer methylphenidate (which increases both dopamine and noradrenaline in both striatum and cortex) reflect modulation of striatal dopamine, we compared the effects of methylphenidate with the effects of the selective D2-receptor antagonist sulpiride, which acts primarily on the striatum where D2-receptors are disproportionately abundant (Hall et al., 1994; Mehta et al., 2003; Westerink et al., 2001).

The two experiments in this large overarching pharmacological PET study were set up to test two complementary hypotheses about dopamine's role in cognitive effort. The first experiment was inspired by neurocomputational modeling work of striatal dopamine (Opponent Actor Learning: OpAL model; (Collins & Frank, 2014)), according to which striatal dopamine increases the weight on the benefit versus cost of options by shifting the balance of activity towards the direct Go pathway away from the indirect NoGo pathway of the basal ganglia. To test this hypothesis, half of the participants included in our study completed an experiment that we recently reported in Westbrook et al. (Westbrook et al., 2020), where participants chose between high-effort and low-effort options while we tracked their eye gaze. In line with the OpAL model (Collins & Frank, 2014), this experiment demonstrated that both methylphenidate and sulpiride boosted the selection of a high- versus low-effort task by increasing the weight on the benefits (monetary payoff) of the high-effort task. This drug effect was present only in participants with lower striatal dopamine synthesis capacity, in line with the hypothesis that dopaminergic drug effects depend on variability in striatal dopamine (Cocker et al., 2012; Cools & D'Esposito, 2011; Froböse et al., 2018).

The other half of the participants included in the large pharmacological PET study completed the experiment reported here. This experiment was motivated by a different hypothesis, derived from the recent opportunity cost theory of cognitive effort (Kurzban et al., 2013; Otto & Daw, 2019), stating that performance of cognitive control tasks is costly, because it requires task focus and persistent task engagement, which interferes with performing potentially rewarding alternative tasks. Inspired by the proposal that the opportunity cost of physical effort, equal to the average reward rate of the environment, corresponds to levels of tonic dopamine (Niv et al., 2007), the opportunity cost of cognitive effort was argued to also be carried by tonic dopamine (Cools, 2015; Kurzban et al., 2013) (but see (Grogan et al., 2020; Zénon et al., 2016)). To test this hypothesis, the current paradigm maximizes sensitivity to the opportunity cost of task engagement by allowing participants to choose between task engagement and leisure (allowing pursuit of unstructured/unspecified opportunities). By contrast,

our previous experiment reported in Westbrook et al. (Westbrook et al., 2020) required choices between high- and low-effort options, thus controlling for opportunity cost.

For the present experiment, we considered two alternative hypotheses. First, we reasoned that prolonging the action of dopamine in the synapse via methylphenidate might potentiate task disengagement by amplifying a putatively dopamine-mediated signal of the opportunity costs of cognitive task engagement (Cools, 2015). By contrast, we also considered the hypothesis that, in line with the OpAL model, methylphenidate might potentiate task engagement by shifting the balance more towards the benefits and away from the costs of cognitive work (Collins & Frank, 2014). Given prior evidence for large individual variability in dopaminergic drug effects, we anticipated that this effect would depend on striatal dopamine synthesis capacity. Although sulpiride can block postsynaptic D2 receptors at higher doses (Eisenegger et al., 2014), we predicted that the direction of sulpiride effects at the dose used in the current study (400mg) would parallel that of methylphenidate's effects due to presynaptic autoreceptor binding, resulting in enhanced dopamine release (Frank & O'Reilly, 2006; Mehta et al., 2008). These predictions were preregistered on https://osf.io/g2z6p/.

Materials and methods

Data and code are available via https://osf.io/4zwu7/.

Participants

Fifty right-handed, neurologically and psychiatrically healthy volunteers were recruited as part of a larger study (detailed study overview in Supplementary information). Participants provided written informed consent and were paid €309 upon completion of the study. The study was approved by the local ethics committee (CMO region Arnhem-Nijmegen, The Netherlands: protocol NL57538.091.16; trial register NTR6140, https://www.trialregister.nl/trial/5959). One participant dropped out during the second day due to nausea, another after four study days due to anxiety, and PET data of two other participants were incomplete (one due to scanner software problems and another due to discomfort during scanning). We analyzed data of the resulting 46 participants (age: mean(SD) = 23.8 (5.9) years; 23 women; body weight: mean(SD) = 71.0(10.1) kg).

General study overview and pharmacological manipulation

A within-subjects, cross-over and double-blind design was used, comprising five sessions. The first day served as an intake session. On the following three pharmacological sessions, participants first completed a working memory delayed response task (24 minutes). To ensure blinding with regard to drug condition, they then received one capsule at each of two different time points: either placebo or 400mg sulpiride at timepoint 1 and either placebo or 20mg methylphenidate at timepoint 2. Participants completed a cognitive effort-discounting choice procedure (duration: 22 minutes) 140 minutes after sulpiride (or the first placebo) administration and 50 minutes after methylphenidate (or the second placebo) administration. Sulpiride plasma concentrations have been found to peak after approximately 3 hours (mean ≈ 2.9h; SD ≈ 1.3h (Helmy, 2013; Wiesel et al., 1980)) and methylphenidate plasma concentrations have been found to peak after approximately 2 hours (mean ≈ 2.2h; SD ≈ 0.8h (Kimko et al., 1999; Spencer et al., 2006; Wargin et al., 1983)). Drug timings were optimized for peak effects during an fMRI paradigm not reported here; near-peak effects were expected during the choice procedure. On the fifth day, participants underwent an [^{18}F]DOPA PET scan to quantify their dopamine synthesis capacity. See Supplementary information for complete task battery and timings.

Behavioral paradigm

Color wheel working memory task

The color wheel task (Figure 2.1A) is a delayed response working memory task assessing two distinct component processes of cognitive control: distractor resistance and flexible updating (Cools, 2016; Papadopetraki et al., 2019). A more detailed description of the paradigm and a discussion on flexibility versus stability are reported in the Supplementary information. The primary research question of this study concerned drug effects on motivation, irrespective of the type of cognitive control process. On each trial, participants had 0.5s to memorize the colors and locations of one to four squares (set-size 1-4), followed by a 2s fixation cross. Then, a new set of colors appeared on screen for 0.5s, accompanied by either the letter 'I' (for 'ignore') or the letter 'U' (for 'update'). In the ignore task-type, participants had to ignore the new colors and keep the previous set in memory. In the update task-type, they had to update their memory with the new set of colors. This was again followed by a fixation cross, which, depending on the task-type, lasted either 2s or 4.5s, ensuring equal delay times between the relevant stimuli (first set for the ignore type and second set for the update type) and the subsequent probe. During this probe phase, participants had 4s to indicate the color of the target square by clicking on the corresponding color on a color wheel. Participants completed 128 trials divided over 2 blocks, with an equal division across set-sizes and task-types.

Choice task

To quantify participants' cognitive motivation, participants completed a choice task (Figure 2.1B) where they successively chose between repeating the color wheel task (redo option) for more money or a no-redo (rest) option for less money, in which participants would be free to do what they wanted for an equal length of time while staying in the testing room. Participants were informed that one of their redo versus no-redo choices would be selected randomly for them to complete. Due to time constraints, and known to the participant, the entire task (i.e. both the monetary bonus and the redo of the color wheel task) was hypothetical. A strong effect of set-size on proportion of redo choices validated the task manipulation, evidencing strong monotonic cognitive load-based discounting (see Results). The hypothetical compensation for the redo option was fixed at €2.00. We assumed that participants would prefer the no-redo over the redo option. However, to also accommodate the possibility of effort seeking, that is, that some participants would unexpectedly prefer the redo option over the no-redo option, we varied the compensation for the no-redo option from €0.10 to €2.20. The redo option was further specified by task-type and set-size, so that participants were instructed that the majority of trials in the redo block would consist of trials of the chosen task-type and set-size. The remainder of the trials would be randomly divided among all task-type and set-size combinations. To account for the stochastic nature of decision-making (Rieskamp, 2008), we opted not to use a titration procedure for arriving at the subjective value (Westbrook et al., 2013), since titration adjusts the offer for the no-redo option based on previous, noisy choices. Instead, we randomly sampled choices across the full value-range in 3 blocks of 96 trials each, equally divided across set-size, task-type and monetary offer for the no-redo option.

PET acquisition and preprocessing

PET scans were acquired on a Siemens PET/CT-scanner at the Department of Nuclear Medicine of the Radboudumc, using an [^{18}F]DOPA radiotracer, produced by the Radboud Translational Medicine department. Participants received 150mg carbidopa and 400mg entacapone 50 minutes before scanning, to minimize peripheral metabolism of [^{18}F]DOPA by decarboxylase and COMT, respectively, thereby increasing signal to noise ratio in the brain. After a bolus injection of [^{18}F]DOPA (185MBq; approximately 5mCi) into the antecubital vein, the procedure started with a low dose CT-scan (approximately 0.75mCi) for attenuation correction of the PET images after which a dynamic PET scan was collected over 89 minutes, divided into 24 frames (4x1, 3x2, 3x3, 14x5 min). PET data (4x4x3mm voxel size; 5mm slice thickness; 200x200x75 matrix) were reconstructed with weighted attenuation correction and time-of-flight recovery, scatter-corrected, and smoothed with a 3mm full-width-at-half-maximum (FWHM) kernel. For registration purposes we acquired a T1-weighted anatomical MRI scan

on the first testing day, using an MP-RAGE sequence (repetition time = 2300ms, echo time = 3.03ms, 192 sagittal slices, field of view = 256mm, voxel size 1mm isometric) on a Siemens 3T MR-scanner with a 64-channel coil. After reconstruction, PET data were preprocessed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). All frames were realigned for motion correction and coregistered to the anatomical MRI-scan, using the mean PET image of the first 11 frames (using the mean image of only the first 11 frames improves coregistration, because these images have a greater range in image contrast in regions outside the striatum). Dopamine synthesis capacity was computed per voxel as [^{18}F]DOPA influx constant per minute (K_i) relative to the cerebellar grey matter reference region using Gjedde-Patlak graphical analysis on the PET frames from the 24th to 89th minute (Patlak et al., 1983). We then extracted average K_i values from three regions of interest (ROIs) – nucleus accumbens, putamen and caudate nucleus – defined using masks based on an independent functional connectivity-analysis of the striatum (Piray et al., 2017) and exactly the same as reported in Westbrook et al. (Westbrook et al., 2020) (Figure 2.1C).

Data analysis

Performance measures on the color wheel task included median absolute degrees of deviance of the response from the correct color (deviance) and median response time (RT) for each participant. Participants' preferences on the choice task were calculated as the proportion of trials on which participants chose the redo option over the no-redo option (proportion redo). Outliers were a priori defined as those who deviated more than three standard deviations from the global mean, which did not result in any exclusions. Repeated-measures ANOVAs were performed using the aov_car function from the afex package (Singmann et al., 2020) in R (version 3.6.0) including drug (placebo, methylphenidate, or sulpiride), task-type (ignore or update) and set-size (ranging from 1 to 4) as within-subjects variables and dopamine synthesis capacity (Ki; measured as the average [^{18}F]DOPA uptake across all voxels within each ROI, mean-centered across participants) as covariate. Unless stated otherwise, we conducted an initial omnibus test including all three drug conditions (drug(3) x task-type(2) x set-size(4) x Ki), followed-up by three planned comparisons between each pair of drug conditions (drug(2) x task-type(2) x set-size(4) x K_i) and the simple three-way interaction under placebo (task-type(2) x set-size(4) x K_i). Separate analyses were run for each ROI – nucleus accumbens, putamen and caudate nucleus. Greenhouse–Geisser corrections were applied when the sphericity assumption was violated. A *p*-value smaller than 0.017 (Bonferroni-corrected for the 3 ROIs) was considered significant. Partial eta squared (η_p^2) and confidence intervals were calculated using the eta.partial.SS function from the MOTE package (Buchanan et al., 2019) in R.

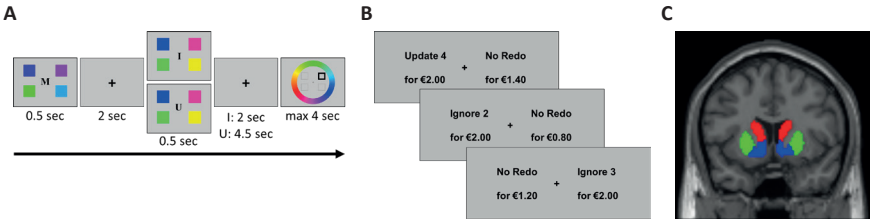

FIGURE 2.1 | **A** – Schematic of the color wheel working memory task. I = 'ignore': participants have to ignore the new squares while still remembering the previous set of squares. U = 'update': participants have to remember the new set of squares and forget the previous set. **B** – Example trial sequence of the cognitive effort discounting choice task. **C** – Coronal view of our regions of interest including the nucleus accumbens (blue), putamen (green) and caudate nucleus (red).

Results

Working memory performance

Before drug intake, participants performed the working memory task. Across sessions and in line with earlier work (Papadopetraki et al., 2019), participants performed poorer when working memory load increased, as indicated by higher deviance (η_p^2 = 0.46, 90% CI [0.34, 0.55], p < 0.001) and longer RTs (η_p^2 = 0.77, 90% CI [0.69, 0.81], p < 0.001). While participants deviated from the target color less on update trials (η_p^2 = 0.50, 90% CI [0.31, 0.66], p < 0.001), their RTs were longer compared with ignore trials (η_p^2 = 0.43, 90% CI [0.23, 0.59], p < 0.001). Both deviance and RT show a significant interaction (deviance: η_p^2 = 0.25, 90% CI [0.14, 0.35], p < 0.001; RT: η_p^2 = 0.09, 90% CI [0.02, 0.16], p = 0.006; Figure 2.2A-B).

There was no main effect of dopamine synthesis capacity on either deviance (caudate nucleus: η_p^2 = 0.01, 90% CI [0.00, 0.12], p = 0.471; putamen: η_p^2 = 0.00, 90% CI [0.00, 0.06], p = 0.795; nucleus accumbens: η_p^2 = 0.01, 90% CI [0.00, 0.09], p = 0.634) or RT (caudate nucleus: η_p^2 = 0.00, 90% CI [0.00, 0.05], p = 0.842; putamen: η_p^2 = 0.01, 90% CI [0.00, 0.10], p = 0.577; nucleus accumbens: η_p^2 = 0.00, 90% CI [0.00, 0.09], p = 0.661), nor did dopamine synthesis capacity interact with any of the other variables.

Methylphenidate increased cognitive motivation

Under placebo, participants exhibited a preference for not repeating any task, as evidenced by the proportion redo being significantly smaller than 0.5 (proportion = 0.38, SD = 0.24; Cohen's d = -0.51, 95% CI [-0.82, -0.20], p = 0.001). As hypothesized, we found a significant effect of drug on proportion redo (main effect of drug with 3 conditions: η_p^2 = 0.10, 90% CI [0.02, 0.21], p = 0.008). This was driven by higher proportion redo under

methylphenidate versus placebo (η_p^2 = 0.15, 90% CI [0.03, 0.33], p = 0.007; Figure 2.2D). There was no difference between sulpiride and placebo (η_p^2 = 0.01, 90% CI [0.00, 0.12], p = 0.443; Figure 2.2D). Numerically, proportion redo was higher under methylphenidate than sulpiride, but this difference did not survive correction for multiple comparisons (η_p^2 = 0.12, 90% CI [0.01, 0.29], p = 0.021). Proportion redo decreased with set-size (η_p^2 = 0.64, 90% CI [0.55, 0.71], p < 0.001; Figure 2.2C). There was no effect of task-type (η_p^2 = 0.03, 90% CI [0.00, 0.15], p = 0.268) and no interaction between task-type and set-size (η_p^2 = 0.03, 90% CI [0.00, 0.08], p = 0.247), nor did drug interact with task-type (η_p^2 = 0.02, 90% CI [0.00, 0.03], p = 0.478) or set-size (η_p^2 = 0.02, 90% CI [0.00, 0.07], p = 0.496).

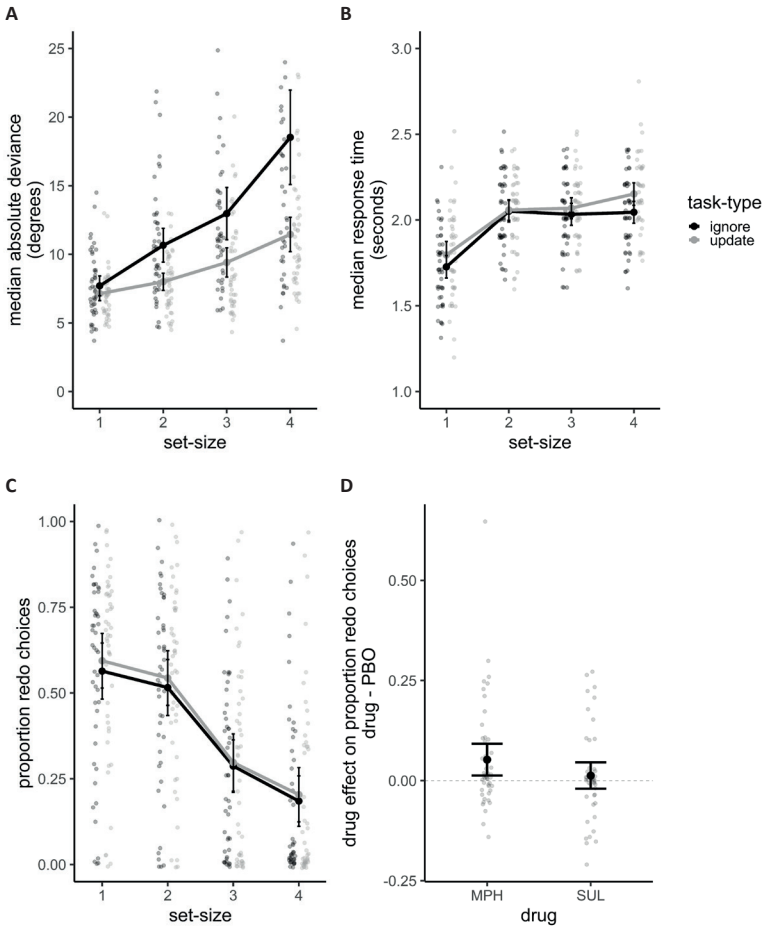

FIGURE 2.2 | **A** – Median absolute deviance, **B** – median response times and **C** – the proportion of trials on which participants chose the redo option across drug sessions plotted as a function of set-size, separately for each task-type. **D** – Drug effect on the proportion of trials on which participants chose the redo option (methylphenidate or sulpiride minus placebo). The methylphenidate-induced effect on proportion redo choices is still significant without the participant showing the greatest effect: $F_{(2.86)}$ = 4.0, p = 0.022. Error bars represent 95% confidence interval around the mean. MPH: methylphenidate; SUL: sulpiride; PBO: placebo.

High-dopamine participants exhibited greater methylphenidate-related increases in cognitive motivation

The effect of methylphenidate on proportion redo depended on dopamine synthesis capacity. This was supported by a significant interaction between drug (methylphenidate, sulpiride, placebo) and dopamine synthesis capacity in the nucleus accumbens (p = 0.009; Figure 2.3B-C; Table 2.1). Participants with higher dopamine synthesis capacity in the nucleus accumbens exhibited greater methylphenidate-induced increases in proportion redo choices than participants with lower dopamine synthesis capacity (p = 0.006). The drug by dopamine synthesis capacity interaction for sulpiride versus placebo (p = 0.314) and for methylphenidate versus sulpiride (p = 0.034) were not significant, after correction for multiple comparisons. Although sub-threshold, interactions in the same direction were found between drug and dopamine synthesis capacity in the putamen and caudate nucleus (Figure 2.3B-C; Table 2.1). A negative association between dopamine synthesis capacity and proportion redo choices under placebo was not significant (Figure 2.3A; Table 2.1). Importantly, supplementary analyses demonstrated that the effect of methylphenidate on proportion redo does not reflect changes in choice randomness, effects on task performance (completed prior to drug administration), or effects on mood and medical symptoms. The effect is reproduced when analyzing 'indifference points' and when controlling for (a failure to counterbalance) session order (Supplementary information).

Drug manipulation does not interact with the benefit of engaging in a cognitive task

Primary analyses on proportion redo choices revealed no significant interactions between drug and the cognitive cost of the task – the set-size. We also explored whether drug effects interacted with the benefit of the task – the monetary payoff for the redo option relative to the no-redo option. Note that the payoff of the redo options was constant throughout the task. To that end, we added, in an additional analysis, the monetary payoff for the no-redo option to our rmANOVA. Because each monetary value was only repeated three times per drug session, task-type and set-size, we divided these values into tertiles so that proportion redo was calculated based on 12 trials. As expected, the monetary payoff had a strong negative main effect on proportion redo (η_p^2 = 0.72, 90% CI [0.62, 0.79], p < 0.001), such that the higher the payoff for the no-redo option, the less often people chose the redo option. Although numerically there was a greater methylphenidate-related increase in proportion redo when the payoff for the no-redo option was lower (i.e. when the benefit for the task was higher), payoff did not significantly interact with drug (η_p^2 = 0.05, 90% CI [0.00, 0.10], p = 0.062) or with the interaction of drug with dopamine synthesis capacity (nucleus accumbens: η_p^2

= 0.02, 90% CI [0.00, 0.04], p = 0.562; putamen: η_p^2 = 0.02, 90% CI [0.00, 0.04], p = 0.513; caudate nucleus: η_p^2 = 0.02, 90% CI [0.00, 0.04], p = 0.456). Thus, while the possibility of unstructured free time comprised unmeasured opportunity costs of engaging in the task, drug manipulation did not reliably affect the sensitivity to the relative, explicit costs or benefits of the redo option.

High-dopamine participants exhibited greater methylphenidate-related slowing of choice latency

Exploratory analyses of choice latency revealed no main effect of drug (η_p^2 = 0.01, 90% CI [0.00, 0.03], p = 0.794). There was a significant interaction between effect of drug on choice latency and dopamine synthesis capacity in the nucleus accumbens (p = 0.005) and putamen (p = 0.002; Table 2.1), which was driven by a difference between methylphenidate and placebo (nucleus accumbens: p = 0.002; putamen: p < 0.001; Table 2.1; Figure 2.4B-C). Methylphenidate slowed people with higher dopamine synthesis capacity and invigorated people with lower dopamine synthesis capacity. No significant interactions between dopamine synthesis capacity and the effect of sulpiride (p > 0.096), or between dopamine synthesis capacity and the difference between methylphenidate and sulpiride (p > 0.021) were observed (Table 2.1). A significant negative association between dopamine synthesis capacity and choice latency under placebo was present in the nucleus accumbens (p < 0.001) and putamen (p = 0.010), but not in the caudate nucleus (p = 0.063), indicating that higher dopamine synthesis capacity was associated with faster responding (Figure 2.4A; Table 2.1).

Positive correlation between drug-induced effects on cognitive motivation and choice latency

Individuals who showed greater methylphenidate-related increases in proportion redo also showed greater methylphenidate-related slowing (Pearson's r = 0.67, 95% CI [0.48, 0.81], p < 0.001). A similar positive correlation was present between the effect of sulpiride versus placebo on choice latency and the drug effect on proportion redo (r = 0.50, 95% CI [0.24, 0.69], p < 0.001).

All region-of-interest based results were corroborated by voxel-wise K_i analyses (Supplementary information), of which the unthresholded statistical maps are available in the NeuroVault.org database at https://neurovault.org/collections/8306/.

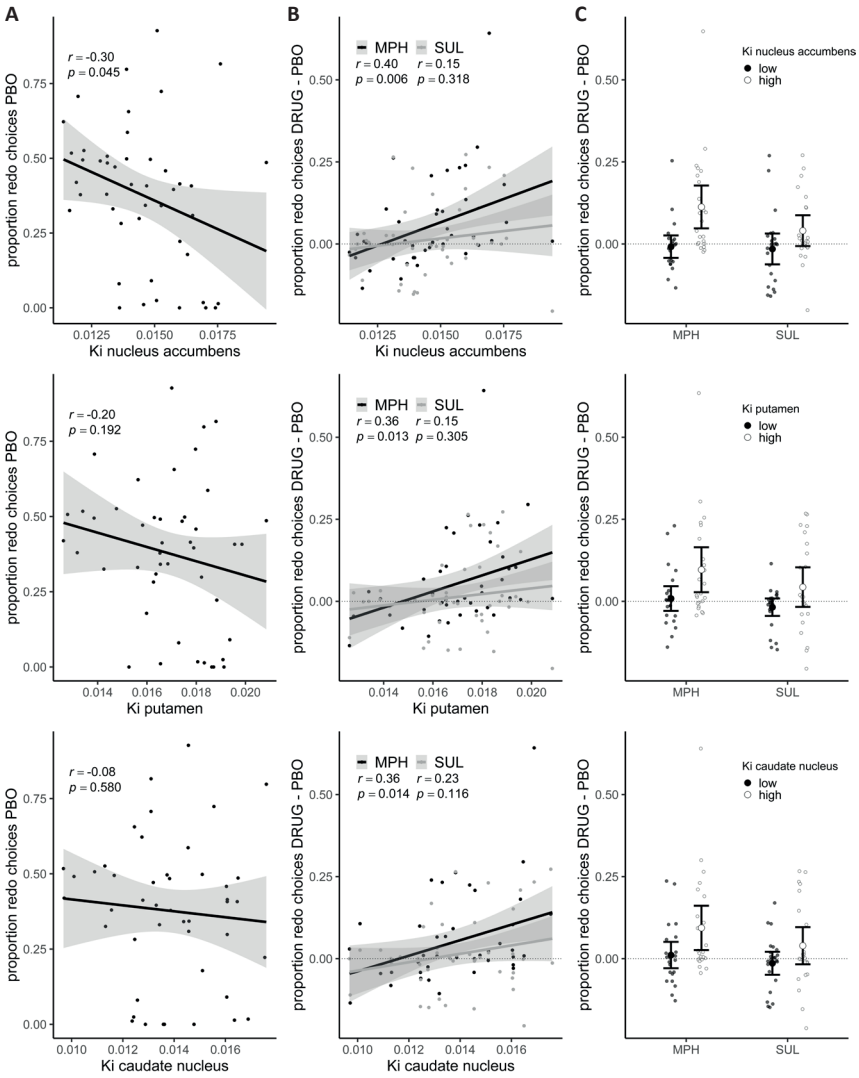

FIGURE 2.3 | Proportion redo choices as a function of dopamine synthesis capacity in the nucleus accumbens (upper panels), putamen (middle panels) and caudate nucleus (bottom panels). *p*-values < 0.017 were considered significant. **A**. Correlation between dopamine synthesis capacity and proportion redo choices under placebo. **B**. Correlation between dopamine synthesis capacity and drug-induced changes in proportion redo choices. Correlation coefficients and *p*-values without the participant showing the greatest methylphenidate-induced effect on proportion redo choices: $r_{\text{nucleus accumbens}} = 0.36$, $p = 0.014$; $r_{\text{putamen}} = 0.41$, $p = 0.005$; $r_{\text{caudate nucleus}} = 0.29$, $p = 0.056$. **C**. Median split on dopamine synthesis capacity for visualization purposes. Shaded areas and error bars represent 95% confidence interval around the mean. PBO = placebo; MPH = methylphenidate; SUL = sulpiride; K_i = [^{18}F]DOPA uptake.

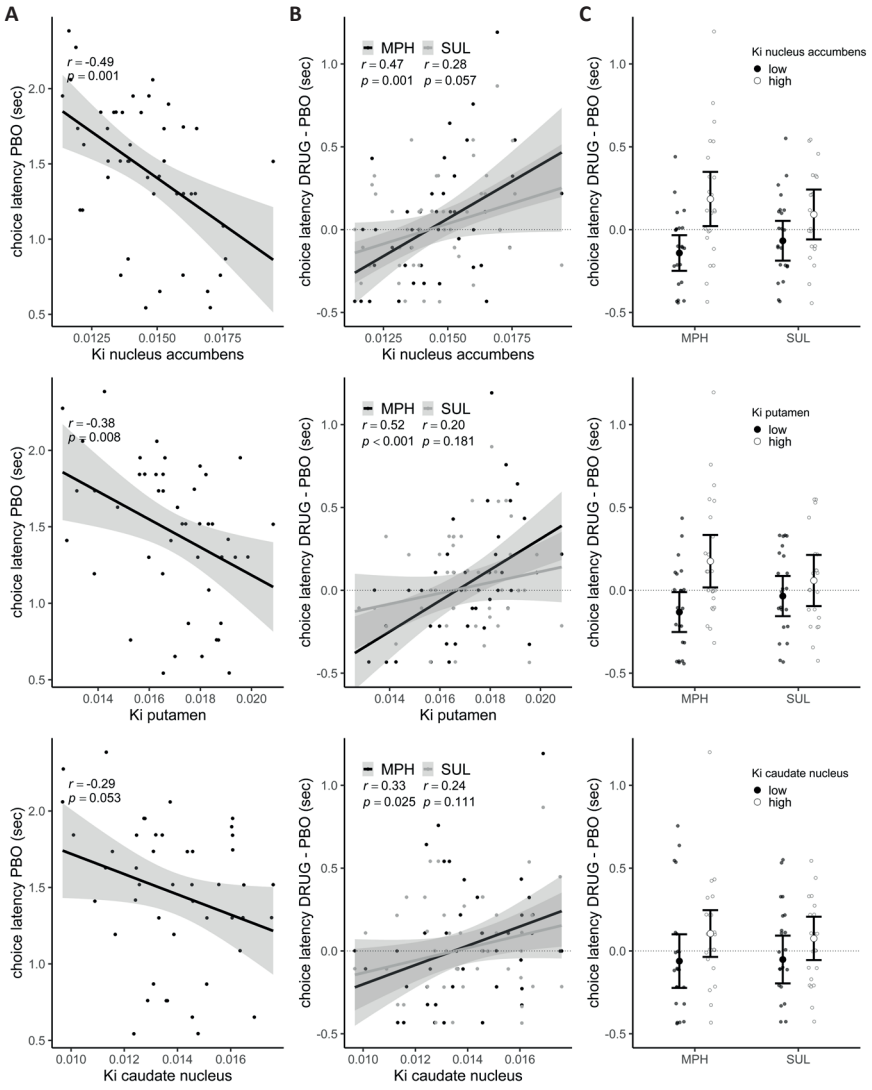

FIGURE 2.4 | Choice latency as a function of dopamine synthesis capacity in the nucleus accumbens (upper panels), putamen (middle panels) and caudate nucleus (bottom panels). *p*-values < 0.017 were considered significant. **A**. Correlation between dopamine synthesis capacity and choice latency under placebo. **B**. Correlation between dopamine synthesis capacity and drug-induced changes in choice latency. **C**. Median split on dopamine synthesis capacity for visualization purposes. Shaded areas and error bars represent 95% confidence interval around the mean. PBO = placebo; MPH = methylphenidate; SUL = sulpiride; K_i = [^{18}F]DOPA uptake.

TABLE 2.1 | Repeated-measures ANOVAs on proportion redo choices and choice latency. Separate analysis for each ROI – nucleus accumbens, putamen and caudate nucleus, including drug, set-size and task-type as within-subjects variables and dopamine synthesis capacity (measured as the mean-centered average [^{18}F]DOPA uptake, K_i) as covariate. Partial eta squared (η_p^2), 90% confidence intervals around η_p^2 and p-values for the interaction between dopamine synthesis and drug are shown, as well as the main effect of dopamine synthesis capacity on the placebo session. MPH = methylphenidate; SUL = sulpiride; PBO = placebo. p-values below a Bonferroni-corrected alpha-value of 0.017 were considered significant.

	Nucleus accumbens		Putamen		Caudate nucleus	
proportion redo choices						
	η_p^2	*p*	η_p^2	*p*	η_p^2	*p*
MPH, SUL, PBO	0.10 [0.02, 0.20]	0.009	0.08 [0.01, 0.18]	0.021	0.08 [0.01, 0.18]	0.025
post-hoc:						
MPH, PBO	0.16 [0.03, 0.34]	0.006	0.13 [0.02, 0.31]	0.012	0.13 [0.02, 0.31]	0.013
SUL, PBO	0.02 [0.00, 0.14]	0.314	0.02 [0.00, 0.15]	0.298	0.06 [0.00, 0.20]	0.114
MPH, SUL	0.10 [0.00. 0.26]	0.034	0.07 [0.00, 0.23]	0.068	0.04 [0.00, 0.17]	0.204
PBO	0.09 [0.00, 0.25]	0.044	0.04 [0.00, 0.17]	0.189	0.01 [0.00, 0.10]	0.574
choice latency						
MPH, SUL, PBO	0.11 [0.02, 0.22]	0.005	0.13 [0.03, 0.24]	0.002	0.05 [0.00, 0.13]	0.113
post-hoc:						
MPH, PBO	0.20 [0.05, 0.38]	0.002	0.22 [0.06, 0.41]	< 0.001	0.08 [0.00, 0.24]	0.056
SUL, PBO	0.06 [0.00, 0.21]	0.096	0.03 [0.00, 0.16]	0.254	0.06 [0.00, 0.20]	0.115
MPH, SUL	0.06 [0.00, 0.21]	0.103	0.12 [0.01, 0.29]	0.021	0.01 [0.00, 0.10]	0.569
PBO	0.22 [0.07, 0.41]	< 0.001	0.14 [0.02, 0.32]	0.010	0.08 [0.00, 0.23]	0.063

Discussion

The present study demonstrates that methylphenidate boosts motivation for cognitive task performance over leisure. This effect was present across the group as a whole but was particularly strong in people with high ventral striatal dopamine synthesis capacity. This finding is consistent with the OpAL model (Collins & Frank, 2014), stating that methylphenidate reduces the weight on the cost of task engagement. Together with the findings reported in Westbrook *et al.* (Westbrook et al., 2020), these data strengthen the link between striatal dopamine and cognitive motivation (Aarts et al., 2011; Mcguigan et al., 2019) and the hypothesis that the cognitive enhancing effect of methylphenidate reflects an increase in motivation. The present study design provides a particularly good test of drug-induced changes in participants' cognitive motivation, rather than capacity, because methylphenidate was administered after the task-performance phase, but before the discounting phase. Moreover, the data firmly establish the pervasive baseline-dependency hypothesis of individual variability in the efficacy of the most commonly used catecholaminergic drug, methylphenidate.

The present paradigm was more sensitive to the motivational boosting effect of methylphenidate, which was observed across the group as a whole, than the paradigm in Westbrook *et al.* (Westbrook et al., 2020), where the effect was detected only in low-dopamine participants. This likely reflects the greater sensitivity of the current paradigm, at baseline, to task avoidance, as evidenced by a strong preference for the rest option. We argue that this increased sensitivity to task avoidance of the present paradigm reflects the increased opportunity cost of task engagement: By choosing the task option, they also chose to forego an opportunity to rest and play with their smartphone and/or laptop. This sensitivity to the opportunity cost at baseline, which tended to be greater in high-dopamine participants, might have rendered greater dynamic range for methylphenidate-related decreases in the weight on the cost. Conversely, Westbrook et al. required choices between a high effort option for more money and a low effort option for less money. This set-up controlled for opportunity costs, and generated a default preference for the high-reward high-effort task. This higher preference for the effortful option at baseline, particularly in high-dopamine participants, might have reduced the range for further increases in the weight on the benefits in those participants. In short, the two paradigms likely differ in their sensitivity to increases in the benefits versus decreases in the costs by methylphenidate. This is supported by the finding that the effect of methylphenidate in the previous experiment, but not the current experiment, interacted with monetary payoff. Critically, the differential sensitivity of the two paradigms to changes in the benefits versus (opportunity and/or effort) costs of cognitive effort might also underlie the observation that methylphenidate effects are greater in high-dopamine

participants in the present experiment but, conversely, in low-dopamine participants in Westbrook *et al.* Future studies might address the question whether the different types of effort costs and benefits implicate dopamine in distinct subregions of the striatum. This hypothesis is raised cautiously by the finding that the effect of methylphenidate on effort selection in the present study depends most strongly on dopamine synthesis capacity in the nucleus accumbens, whereas the effect in Westbrook *et al.* depends most strongly on dopamine in the caudate nucleus.

According to the OpAL model (Collins & Frank, 2014), methylphenidate might have reduced the cost of cognitive effort in this study by decreasing activity in the NoGo pathway of the basal ganglia. An alternative account of the observed effect is motivated by the "inverted-U" hypothesis of dopamine, which states that dopaminergic drugs shift dopamine levels from suboptimal to optimal levels in low-dopamine individuals, while shifting them from optimal to supra-optimal levels in high-dopamine individuals (Cools & D'Esposito, 2011). Specifically, methylphenidate might have decreased task motivation in low-dopamine subjects by increasing the (intrinsic) value of the rest option, while increasing task motivation in high-dopamine subjects by detrimentally "overdosing" the (intrinsic) value of the rest option.

Exploratory analyses revealed a strong negative association between choice latency and dopamine synthesis capacity under placebo. While methylphenidate sped up choices of participants with low dopamine synthesis capacity, it slowed choices of participants with higher dopamine synthesis capacity. Intriguingly, these striatal dopamine-dependent effects of methylphenidate on choice latency correlated with the effects of methylphenidate on cognitive effort choice. One explanation of this effect is that the strength of the default preference for no-redo was strongest for people with high dopamine synthesis capacity. Because these participants showed the largest shift away from a default preference on methylphenidate, they might have experienced greater choice conflict, accounting for their slowing.

The clinical implications of the current results for populations who commonly get prescribed methylphenidate have yet to be determined. Studies of the relationship between impulse control disorders and striatal dopamine synthesis capacity have produced contrasting results, with enhanced capacity in pathological gamblers (Holst et al., 2018), conflicting results in substance abusers (Bloomfield et al., 2014; Heinz et al., 2005; Rademacher et al., 2016; Tiihonen et al., 1998) and if anything reduced capacity in ADHD patients (Ernst et al., 1998; Ludolph et al., 2008).

A limitation of the current pharmacological PET study is that it does not allow us to directly address the neural locus of methylphenidate's effect. The finding that the

effects of methylphenidate were associated with striatal dopamine synthesis capacity suggests that methylphenidate acted on the striatum to modulate cognitive motivation. However, given that [^{18}F]DOPA uptake signal is too low in the prefrontal cortex, we cannot exclude the possibility that the variation in nigrostriatal dopamine synthesis capacity is paralleled by variation in prefrontal dopamine levels. An additional prefrontal locus of effect is also consistent with the absence of significant effects of sulpiride, which acts selectively on dopamine D2-receptors that are particularly abundant in the striatum. In future studies pharmacology and PET should be combined with functional magnetic resonance imaging to isolate the neural locus of the dopamine-dependent effects of methylphenidate on cognitive motivation.

The finding that the effects of methylphenidate, which blocks both dopamine and noradrenaline transporters (Kuczenski & Segal, 2001; Scheel-Krüger, 1971), were not accompanied by significant effects of the selective D2-receptor antagonist sulpiride is surprising. First, previous research has established that the present dose of sulpiride is effective at approximately 2 hours after intake, indexed in terms of both sulpiride plasma concentrations (Helmy, 2013; Wiesel et al., 1980) and behavioral effects on reversal learning (Van Der Schaaf et al., 2014). Second, the exact same dose of sulpiride did have a significant effect in Westbrook *et al.* (Westbrook et al., 2020), where the exact same study protocol was applied. This might lead some to ask whether the current effects reflect a modulation of noradrenaline instead of dopamine (Aston-Jones & Cohen, 2005; Gilzenrat et al., 2010; Hopstaken et al., 2015; Rajkowski et al., 1993; Van den Brink et al., 2016). However, given the lack of sulpiride-related changes in physiological or subjective report measures (Supplemental information), we cannot exclude the possibility that the drug manipulation did not alter behavior on the current task due to for example, suboptimal timing or dosing. It is known that sulpiride can bind to both pre- and postsynaptic D2 receptors, with low doses (50-150mg) primarily binding pre-synaptically and high doses (>800mg) primarily binding post-synaptically (Chavanon et al., 2013; Frank & O'Reilly, 2006; Serra et al., 1990). The 400mg used in the current study might thus have had mixed pre- and postsynaptic effects, cancelling each other out. Nevertheless, the pattern of sulpiride effects resembled that of methylphenidate, with the difference between the two drugs not reaching significance. It is uncertain whether this represents a true difference between the effects of sulpiride and methylphenidate, a suboptimal dose that had a presynaptic effect in most participants but was sufficiently high to have a primarily postsynaptic effect in some participants, or rather a lack of statistical power to detect sulpiride-induced effects. Given that methylphenidate's effects were predicted by [^{18}F]DOPA uptake in the striatum (which does not contain any noradrenaline receptors), and the resemblance between the pattern of effects of methylphenidate and sulpiride, we argue that they likely reflect modulation of dopamine rather than noradrenaline. Indeed this conclusion

also concurs with prior evidence that methylphenidate's enhancing effects correspond with changes in midbrain dopamine release (Del Campo et al., 2013).

In conclusion, this study suggests that methylphenidate reduces the cost of mental labor by increasing striatal dopamine, thus strengthening the motivational account of methylphenidate's effects on cognition.

Acknowledgments

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Supplemental methods

Task battery

The current experiment was part of a larger study (*N* = 100; https://www.toetsingonline.nl/to/ccmo_search.nsf/fABRpop?readform&unids=3EF826A78F26D323C12585A50015752A). The first twenty-five women and twenty-five men completed the color wheel task. A description of the task battery, timings and randomization of the drug sessions can be found in Tables S2.1-3.

The study consisted of five sessions, with an interval of at least one week between each session. The first study day served as an intake on which participants were screened for inclusion criteria (see below), underwent an anatomical MR scan, and completed several baseline measures (Table S2.4). On the following three pharmacological sessions participants first completed a working memory delayed response task, then they received an oral administration of either 20 mg of methylphenidate, or 400 mg of sulpiride, or a placebo. Methylphenidate is a catecholamine-transporter blocker, which reduces the reuptake of catecholamines, including dopamine and norepinephrine, thereby increasing their availability in the synapse. Sulpiride is a selective D2 receptor antagonist that acts specifically on the dopamine system. Timings of drug administration were optimized for peak drug effects during the fMRI paradigm (not reported here; Table S2.2): methylphenidate plasma concentrations peak after 2 hours (Kimko et al., 1999) and sulpiride plasma concentrations peak after 3 hours (Wiesel et al., 1980). Near-peak effects were expected during the task of interest. After drug administration participants completed a cognitive effort-discounting choice procedure. Blood pressure, heart rate, and ear temperature were measured three times during the day for monitoring and safety reasons. At the same time-points, medical symptoms and mood measures were assessed three times on each session: at the start of each session, 20 minutes before the discounting task and at the end of the session (Table S2.5). On the fifth day, participants underwent an [^{18}F]DOPA PET scan to quantify their dopamine synthesis capacity and completed several baseline measures (Table S2.4).

TABLE S2.1 | Task battery

DAY 1: INTAKE	DAY 2-4: PHARMACOLOGICAL-fMRI	HOME: QUESTIONNAIRES	DAY 5: PET SCAN
HEALTH SCREENING	**COGNITIVE ASSESSMENT**	**PERSONALITY ASSESSMENT**	**COGNITIVE ASSESSMENT**
Psychiatric assessment	**Executive functions**	Impulsivity (BIS-11A)	**Executive functions**
M.I.N.I Plus 5.0.0	Color wheel working memory task[1]	Behavioral inhibition/activation	Digit span (Version B)
Physiological measures	N-back working memory task[1]	Need for Cognition	**Intellectual functioning**
Electrocardiogram (ECG)	**Cognitive motivation**	Depression inventory (BDI)	Fluid intelligence (matrix reasoning)
Heart rate / blood pressure	Cognitive effort discounting task	Creativity scale (K-DOCS)	**Motivation/learning**
Body temperature	Reward processing		Pavlovian to instrumental transfer task
Spontaneous eye blink rate	Reinforcement learning and working memory (RLWM)		
MRI	Creativity		**DOPAMINE SYNTHESIS CAPACITY**
Anatomical T1 scan	Alternative uses task		**Positron emission tomography (PET)**
	Remote association task		Carbidopa and entacapone intake
COGNITIVE ASSESSMENT	Alternative names task		[^{18}F]DOPA bolus injection
Executive functions			
Digit span (version A)	**fMRI**		
Listening span	**Reward processing and motivation**		
Intellectual functioning	Reversal learning task (RL)		
Crystalized IQ (NLV)	Monetary Incentive Delay task (MID)		
	SOMATIC MEASURES		
	Heart rate / blood pressure		
	Body temperature		
	MOOD ASSESSMENT		
	Positive and negative affect scales (PANAS)		
	Visual analogue scale (VAS)		

[1] First fifty participants completed the color wheel task (data reported here) while the second fifty completed the N-back task (Westbrook et al., 2020). M.I.N.I.: Dutch M.I.N.I. International Neuropsychiatric Interview 5.0; NLV: Dutch reading test; BIS-11A: Barratt Impulsiveness Scale; BDI: Beck Depression Inventory II; K-DOCS: Kaufman Domains of Creativity Scale.

TABLE S2.2 | Pharmacological-fMRI session – timings

Description	Sulpiride	Methylphenidate
Screening	-70	-160
Somatic and mood measures	-65	-155
BEH: color wheel or N-back	-40	-130
Capsule 1: SUL/PBO	0	-90
Rest	1	-89
Capsule 2: MPH/PBO	89	0
MRI: screening	105	15
Somatic and mood measures	120	30
BEH: cognitive effort discounting task	140	50
MRI: installment	170	80
MRI: RL	185	95
MRI: MID	215	125
Lunch	235	145
BEH: RLWM	250	160
BEH: Creativity	290	200
Somatic and mood measures	308	218
End study day	328	238

Timings are in minutes, where T = 0 is the time of drug intake. Participants either received sulpiride (SUL) followed by placebo (PBO), PBO followed by methylphenidate (MPH) or PBO twice in a within-subjects, cross-over double-blind design. BEH: behavioral testing; MRI: functional magnetic resonance imaging. RL: reversal learning task; MID: monetary incentive delay task; RLWM: reinforcement learning and working memory task.

TABLE S2.3 | Number of participants per drug order.

Day 2	Day 3	Day 4	No. Participants
MPH	SUL	PBO	10
MPH	PBO	SUL	10
SUL	MPH	PBO	6
SUL	PBO	MPH	7
PBO	MPH	SUL	6
PBO	SUL	MPH	7

PBO: placebo; MPH: methylphenidate; SUL: sulpiride

TABLE S2.4 | Demographic and background characteristics of participants.

	Characteristic	Measure / unit				
Demographics	Gender	Women / men (number)	23/23			
			Min	**Max**	**Mean**	**SD**
	Age	years	18	43	23.8	5.9
	Body weight	kg[1]	48.0	96.0	71.0	10.1
Neuropsychological	Working memory capacity	Listening span: total span	0	6.5	4.2	1.5
assessment		Digit span[2]:				
		Forward	4.5	12.5	8.2	1.9
		Backward	3.5	11.5	7.4	2.1
	Verbal intelligence	NLV[2]	69.5	98.0	84.8	5.9
	Fluid intelligence	WAIS-IV-NL	9	22	16.8	3.1
Self-report	Trait impulsivity	BIS-11[3]: total score	41.3	83.8	66.4	8.7
questionnaires	Need for Cognition	NCS	41	81	61.2	9.0
	Depressive symptoms	BDI	0	13	3.7	3.4
	Behavioral inhibition/activation	BIS/BAS: total score	22	48	39.3	5.2
	Creativity	K-DOCS: total score	2.2	5	3.0	0.5

Minimum and maximum score, mean and standard deviation (SD) of demographic and background characteristics of participants included in the behavioral analyses. Neuropsychological assessment included the Dutch reading test (NLV; (Schmand et al., 1991)), listening span task (Daneman & Carpenter, 1980; Salthouse & Babcock, 1991), digit span test (forward and backward; (Wechsler et al., 2008)), and the matrix reasoning subtest of the WAIS-IV-NL (Wechsler et al., 2008). Questionnaires included the Barratt Impulsiveness Scale (BIS-11A; (Barratt, 1994)), Need for Cognition Scale (NCS; (Cacioppo et al., 1984)), Beck Depression Inventory II (BDI-II; (Beck et al., 1996)), Behavioral Inhibition Scale/Behavioral Activation Scale (BIS/BAS; (Carver & White, 1994)) and the Kaufman Domains of Creativity Scale (K-DOCS; (Kaufman, 2012)). *N* = 46. [1]4 missing values. [2]1 missing value. [3]The BIS-11A, an earlier version of the BIS-11 (Patton et al., 1995), was inadvertently sent to the participants. We converted the scores to BIS-11 (Lijffijt, n.d.) to be able to compare impulsivity scores with earlier studies. Scores are comparable with earlier observations in healthy populations, e.g. Froböse et al., 2018 (Froböse et al., 2018): Listening span: mean = 4.8; Digit span forward: mean = 8.3; Digit span backward: mean = 7.2; BIS-11: mean = 61.8; NCS: mean = 63.3; BDI: mean = 3.6; BIS/BAS: mean total score = 39.7. Cacciaglia et al., 2018 (Cacciaglia et al., 2018): WAIS-IV matrix reasoning: mean = 16.3. Pretz & Kaufman, 2015 (Pretz & Kaufman, 2017): K-DOCS total score: mean = ~3.2. Timmer et al., 2017 (Timmer et al., 2018): NLV-IQ mean = 100.7, equivalent to NLV mean = ~88.0.

TABLE S2.5 | Medical symptoms and mood measures

	PBO			MPH			SUL		
	time 1	**time 2**	**time 3**	**time 1**	**time 2**	**time 3**	**time 1**	**time 2**	**time 3**
Heart rate	68.0 (10.7)	55.1 (8.7)	61.1 (9.6)	68.3 (11.7)	53.7 (7.9)	67.9 (11.8)	68.5 (11.6)	54.8 (8.4)	61.3 (10.2)
Blood pressure: systolic	116.2 (10.0)	112.9 (9.6)	115.4 (9.0)	116.7 (8.2)	114.7 (9.6)	120.0 (9.9)	115.9 (9.5)	114.2 (9.0)	115.4 (8.6)
Blood pressure: diastolic	62.9 (6.8)	63.8 (7.5)	61.8 (6.3)	62.3 (6.4)	64.9 (7.4)	65.4 (7.2)	61.6 (6.7)	62.6 (6.4)	60.9 (5.4)
Ear temperature	35.8 (0.5)	35.9 (0.4)	36.1[1] (0.4)	35.9 (0.5)	36.0 (0.5)	36.2 (0.5)	35.8[1] (0.5)	36.0 (0.5)	36.0 (0.5)
VAS: medical	11.7 (3.7)	11.2 (3.4)	11.2 (2.6)	13.4 (4.5)	12.2 (3.4)	12.4 (4.1)	11.5 (3.0)	11.3 (3.4)	11.2 (3.2)
PANAS: positive affect	28.9 (6.5)	27.3 (7.4)	25.5 (7.8)	27.8 (7.9)	27.7 (7.0)	27.2 (8.3)	28.1 (7.2)	27.7 (7.4)	24.8 (7.7)
PANAS: negative affect	11.5 (2.3)	11.0 (1.9)	10.8 (1.5)	12.0 (2.7)	11.1 (2.2)	11.1 (2.1)	11.8 (2.1)	11.4 (2.2)	11.9 (1.9)
VAS: alertness	7.1 (1.5)	7.2 (1.5)	6.6 (2.0)	6.8 (1.6)	7.2 (1.3)	7.0 (1.7)	7.2 (1.4)	7.1 (1.4)	6.4 (1.9)
VAS: calmness	7.7 (1.4)	8.0 (1.4)	8.0 (1.3)	7.8 (1.3)	7.9 (1.4)	7.5 (1.7)	7.4 (1.3)	7.8 (1.6)	8.0 (1.5)
VAS: contentedness	8.0 (1.1)	7.9 (1.1)	7.9 (1.2)	7.8 (1.4)	8.0 (1.3)	8.0 (1.3)	7.9 (1.3)	8.1 (1.1)	7.9 (1.2)

Mean (SD) scores for heart rate, blood pressure (systolic and diastolic), ear temperature, medical symptoms visual analogue scale and mood measures: Positive and Negative Affect Scale (PANAS); Bond and Lader Visual Analogue Scales (alertness, calmness and contentedness) at each timepoint (baseline, start testing, end testing) for each drug (PBO = placebo; MPH = methylphenidate; SUL = sulpiride). *N* = 46. [1] 1 missing value.

Inclusion criteria

Inclusion age range was 18–45 years old and participants had to be native-Dutch speakers, right-handed, had to have normal or corrected-to-normal vision and could not be color-blind. Assessment for inclusion on the first testing day comprised a medical screening, assessing blood pressure (systolic BP: 95-140 mm Hg; dystolic BP: 50-95 mm Hg), heart rate (45-120 bpm) and electrocardiography (QTC-interval M: <450 ms; F: <460 ms; PR-interval: <250 ms), as well as a systematic psychiatric screening interview (M.I.N.I. Plus 5.0.0) assessing psychiatric symptoms, such as major depression, dysthymia, suicidality, (hypo) mania, panic disorder, agoraphobia, social anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, alcohol abuse and dependence, psychoactive substance use disorders, psychotic disorder, anorexia nervosa, bulimia nervosa, generalized anxiety disorder, and attention deficit/hyperactivity disorder. Participants could not have a diagnosis (or history) of relevant psychiatric, neurological, endocrine, or neuroendocrine treatment; frequent autonomic failure; clinically significant hepatic, cardiac, obstructive respiratory, renal, cerebrovascular, cardiovascular, metabolic, ocular or pulmonary diseases/disorders; alcohol or drug dependence; epilepsy; Raynaud's syndrome; one first degree, or two or more second degree family members with history of sudden death of ventricular arrhythmia; history of over the counter medication within the last two months or prescribed medication within the last month prior to the study; regular use of corticosteroids; habitual smoking; diabetes; abnormal hearing or (uncorrected vision); glaucoma; irregular sleep/wake rhythm; possible pregnancy and no appropriate contraception. Participants had to abstain from cannabis throughout the course of the experiment, including 2 weeks before the start of the first pharmacological session, and were required to abstain from alcohol 24 hours and psychotropic medication and recreational drugs 72 hours before each session.

Detailed description of the behavioral paradigm

Before drug administration, participants completed a short color sensitivity task (1 minute) and a color wheel working memory task to familiarize participants with the type and level of cognitive control (24 minutes). After drug-intake they completed a cognitive effort-discounting choice task (22 minutes) to quantify the subjective value (and effort costs) of the color wheel working memory task. All tasks were performed on a computer running on Windows 7 and a screen resolution of 1920x1080p. The background color for all tasks was grey (R: 200 G: 200 B: 200). All tasks were programmed in MATLAB version 2016a, using Psychophysics Toolbox Version 3.0.12.

Color sensitivity task

The color sensitivity task measured the ability to detect and distinguish the colors in the main task. A color wheel was presented in the middle of the screen and participants had to match the color of a square in the center of the wheel with the corresponding color on the wheel, by clicking on the color wheel. This task consisted of 12 trials and performance on the color sensitivity task was successful if the average deviation of the response from the correct color was below 15 degrees. If participants failed the first time, the color sensitivity task would be assessed again. Participants would be excluded if they failed the color sensitivity task twice (no participants failed the sensitivity test).

The color wheel was created by placing a background-colored circle with a radius of 362p on a circle with a radius of 486p that contained 512 successive colors. By placing the smaller circle over the bigger circle, a colored ring was created. Each color had an angle width of 0.7 degrees and was created with the HSV MATLAB color map. The color of the square was one of the 512 colors from the color wheel. After participants responded, a black line appeared that marked and confirmed the response. The black line consisted of a 0.4-degree arc, placed on the color wheel. Additionally, feedback conveying the deviance (the degrees the response deviated from the correct color) was given if the deviance was below 10 degrees: e.g. 'Good job! You deviated only 4 degrees!' and by a second black arc that marked the correct location of the color. If the deviance was more than 10 degrees, the feedback only consisted of the second black arc. Participants were instructed to answer precisely, but not to take too much time to respond. There was no maximum response time. To test a wide variation of colors from the color wheel, the color wheel was divided into 12 parts, from now on referred to as color pies. From each color pie, one color was chosen at random to be presented in the center of the color wheel. Both the color of the square and the orientation of the color wheel were randomized across participants.

Color wheel working memory task

The color wheel task (Figure 2.1A) is a delayed response task of working memory that distinguishes between distractor resistance and flexible updating, based on a paradigm introduced by Zhang and Luck (Zhang & Luck, 2008). Participants had to match a color that was held in working memory to a color wheel on the screen. Each trial was preceded by a centered black dot for 0.5s, which signaled the start of a new trial. On each trial, colored squares were presented in the middle of the screen, with the letter M in the middle, which stood for 'memorize'. During this encoding phase, participants had 0.5s to memorize the colors of the squares, after which there was a delay of 2s. During this delay, a fixation cross was presented in the middle of the screen. Then, during the

interference phase, a new set of colored squares appeared on screen, with one of two letters in the center. 'I' stood for 'ignore': participants had to ignore the new squares while still remembering the previous set of squares. 'U' stood for 'update': participants now had to update the colors of the squares, that is, remember the new set of squares and forget the previous squares. The new set of squares remained on screen for 0.5s, followed by a second delay phase. Depending on the task-type, distractor resistance (ignore) or flexible updating (update), this delay lasted either 2s or 4.5s, respectively, to have the same length of time between the relevant stimuli (encoding phase for the ignore type and interference phase for the update type) and the last phase, the probe phase. During this probe phase, a color wheel appeared in the center of the screen, containing frames of colorless squares, one of which was marked. Participants had 4s to indicate the target color of the marked square by clicking on the corresponding color on the color wheel. For example, if the upper right frame was marked, and the condition was ignore, participants had to indicate the color of the upper right square during the encoding phase. When a response was made, a black line appeared on the color wheel at the location where the mouse click was made, remaining on screen until 4s had passed since the appearance of the color wheel. No feedback was given on accuracy. If participants did not respond within 4s, a message was presented for 0.5s in the center of the screen: 'Please respond faster!' Participants were instructed to keep their eyes fixed on the center of the screen during the entire task.

The number and locations of the squares were the same in each phase, but differed over trials, ranging from 1 to 4 squares, allowing us to assess effects of cognitive load (from now on referred to as set-size). All combinations of set-size (ranging from 1-4) and task-type (ignore or update) were repeated 16 times, which resulted in 128 trials divided over two blocks. The task was preceded by 16 practice trials. On these practice trials, feedback conveying the deviance (the degrees the response deviated from the correct color, with a maximum of 180 degrees) was given if the deviance was below 10 degrees: e.g. 'Good job! You deviated only 4 degrees!' and by a second black line that marked the correct location of the color. If the deviance was more than 10 degrees, the feedback only consisted of the second black line. Feedback duration was 0.7s. To control for possible effects of different colors, the colors that were presented during the encoding phase of ignore trials were the same as the colors that were used during the interference phase of update trials. Additionally, the target colors were the same for both conditions. To control for possible location effects, the locations of the squares were allocated equally across trials and the location of the marked frame, and thus the target, was balanced across conditions. Additionally, the orientation of the color wheel was randomized across trials. Trial order was the same for each participant.

Choice task

To quantify participant's preference for the task versus rest, participants completed a choice task where they repeatedly chose between a cognitively effortful (redo) option for more money and a leisure (no-redo) option for less money (Figure 2.1B). A redo choice implied that they preferred to complete another block of the color wheel task after completing the choice task. By choosing the no-redo option they indicated that they preferred to be free to do what they wanted, such as using their phone or the computer, for an equal length of time as another round of the color wheel task, while staying in the testing room. Participants were informed that their monetary bonus and the difficulty of the working memory task would depend on their choices during the choice task, because one of their choices would be randomly selected. Due to time constraints and to avoid transfer effects of experiencing the color wheel task under drug to future sessions, both the monetary bonus and the redo of the color wheel task were hypothetical, and participants were instructed accordingly. The rationale for this instruction was that it pre-empted gradual learning that the redo phase was hypothetical, invalidating comparison between the three sessions. Despite its hypothetical nature, the task manipulation and sensitivity to cognitive effort was validated by evidence for strong monotonic, set size-dependent discounting (see Results). The hypothetical compensation for the redo option was fixed at €2.00. The compensation for the no-redo option varied from a minimum of €0.10, and then from €0.20 to €2.20, with intervals of €0.20. The redo option was further specified by a task-type (ignore or update) and a set-size (1-4), which meant that most of the redo block would consist of trials of that task-type and set-size. The remainder of the trials would be divided among all task-type and set-size combinations. The task was divided into three blocks, with a break in between the blocks. Each block featured each unique combination of task-type, set-size and monetary compensation for the no redo option (€0.10-€2.20) in random order, which resulted in 96 trials per block and 288 trials in total. On each trial participants had 4s to respond. They were told that to receive the bonus, their performance during the redo block would have to be similar to their performance during the earlier blocks and that this meant that they had to put effort into doing the redo block, but not that they always had to be correct. This was conveyed to minimize differences in preference for a condition due to earlier performance differences.

Supplemental results

Here we report the results from a number of supplementary control analyses to explore the primary effects of interest reported in the main manuscript. These exploratory analyses were conducted to confirm that the effects that were established to be significant in our primary analyses of interest are physiologically plausible (i.e. by the supplementary voxel-wise PET analyses) and that they do not reflect any factors of no interest. While we report confidence intervals, effect sizes and p-values for these supplementary analyses, we note that these should be interpreted with caution, given that these analyses were not designed to test our primary hypotheses or to test new additional hypotheses, and were thus not corrected for multiple comparisons, but rather served to double-check already established effects.

Voxel-wise PET analyses

We conducted voxel-wise analyses in addition to our primary region-of-interest analyses to assess the physiological plausibility of the link between drug effects on choice behavior (proportion redo choices and choice latency) and striatal dopamine synthesis capacity (K_i influx constant). To this end, the individual K_i maps were spatially normalized to MNI space and smoothed using an 8mm FWHM kernel. We restricted our search, following prior procedures (Sescousse et al., 2018), to one region of interest comprising all voxels that exhibited a K_i value of 3 standard deviations above the global mean. This region of interest included the striatum and midbrain (8993 voxels; Figure S2.1). Statistical significance was defined as family-wise error (FWE) corrected $p<0.05$ at peak coordinate, after small volume correction for all voxels within the region of interest. Note that the group-based [^{18}F]DOPA mask was calculated based on the larger study group excluding drop-outs (N = 94).

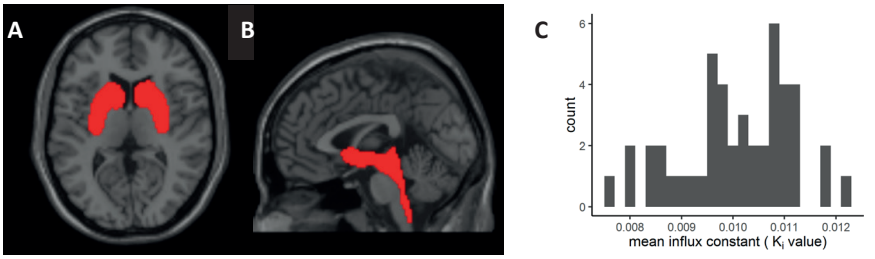

Figure S2.1 | **A** – Axial and **B** – sagittal view of the group-based small volume mask including all voxels with a K_i value of > 3 SD from the global mean. **C** – Histogram of mean K_i value within the group-based mask. Count represents number of participants. N = 46. The mean K_i values varied between 0.00768 and 0.01228. These values are comparable with previous reports (van Holst et al., 2018).

High-dopamine participants exhibited greater methylphenidate-related increases in cognitive motivation

In accordance with our region-of-interest based results, voxel-wise analyses revealed a positive correlation between dopamine synthesis capacity and the methylphenidate effect on overall proportion redo choices (Figure S2.2B; Table S2.6). Participants with higher dopamine synthesis capacity exhibited greater methylphenidate-induced increases in proportion redo choices than participants with lower dopamine. The correlation with midbrain dopamine synthesis capacity survived *FWE*-correction. Although not surviving *FWE*-correction, positive correlations with the methylphenidate effect were also found in the nucleus accumbens, putamen, and caudate nucleus. There was no association between the effect of sulpiride on proportion redo choices and dopamine synthesis capacity (Figure S2.2C) and no voxels correlated significantly with the difference in proportion redo choices between methylphenidate and sulpiride (Figure S2.2D; Table S2.6). The correlation between dopamine synthesis capacity and proportion redo choices under placebo was not significant (Figure S2.2A; Table S2.6).

High-dopamine participants exhibited greater methylphenidate-related slowing of choice latency

The effect of methylphenidate on choice latency correlated positively with dopamine synthesis capacity in the midbrain, left caudate nucleus and right putamen (Figure S2.2F; Table S2.6), indicating that methylphenidate slowed people with higher dopamine synthesis capacity and invigorated people with lower dopamine synthesis capacity. No significant correlation between dopamine synthesis capacity and the effect of sulpiride was observed (Figure S2.2G; Table S2.6) and no voxels correlated significantly with the difference in choice latency on the methylphenidate and the sulpiride session (Figure S2.2H; Table S2.6). Dopamine synthesis capacity correlated negatively with choice latency under placebo in the left caudate nucleus and midbrain (Figure S2.2A; Table S2.6), indicating that higher dopamine synthesis capacity was associated with faster responding.

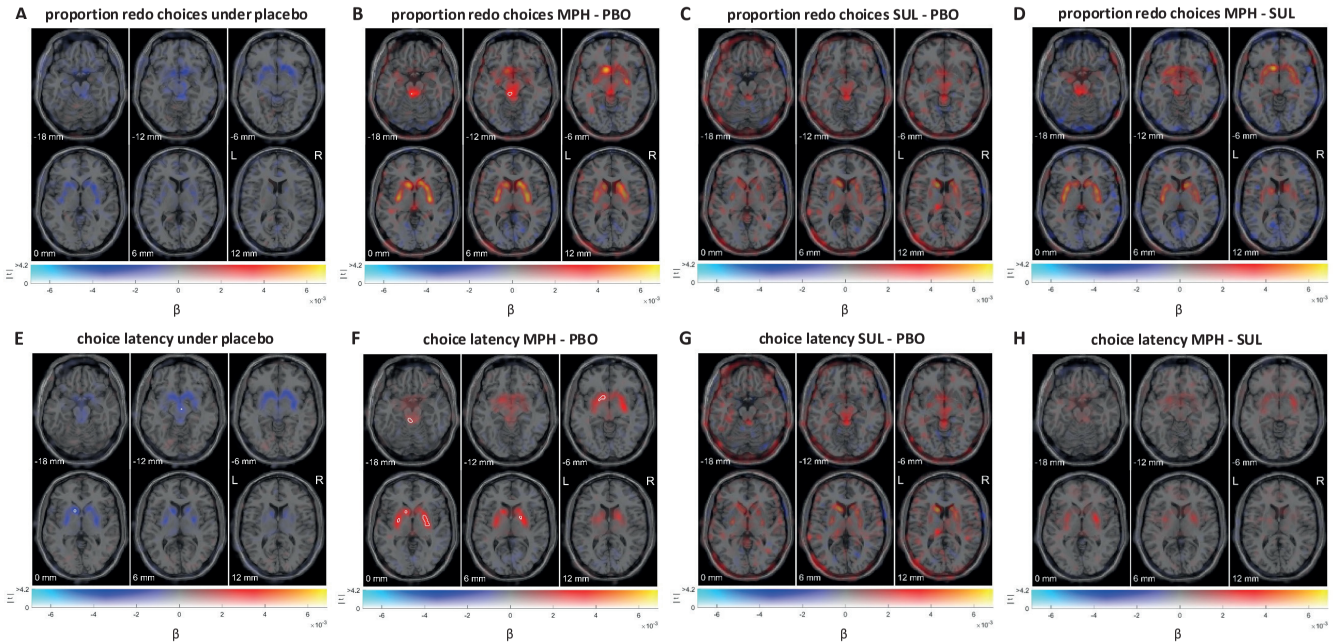

FIGURE S2.2 | Voxels showing a positive (red) or negative (blue) regression coefficient on (**A**) the proportion redo choices under placebo (PBO), (**B**) the effect of methylphenidate (MPH) versus placebo on proportion redo choices, (**C**) the effect of sulpiride (SUL) versus placebo on proportion redo choices, (**D**) the effect of methylphenidate versus sulpiride on proportion redo choices, (**E**) choice latency under placebo, (**F**) the effect of methylphenidate versus placebo on choice latency, (**G**) the effect of sulpiride versus placebo on choice latency, (**H**) the effect of methylphenidate versus sulpiride on choice latency. The brain maps are dual-coded and simultaneously display the contrast estimate (x axis) and t values for the drug contrast (y axis). The hue indicates the size of the contrast estimate, and the opacity indicates the height of the t value. Significant clusters (peak-level corrected, FWE, $p<0.05$) are encircled in white. The z coordinates correspond to the standard MNI brain. Neuroimaging data are plotted using a procedure introduced by Allen et al. (Allen et al., 2012) and implemented by Zandbelt (Zandbelt, 2017).

TABLE S2.6 | Brain regions exhibiting correlations between dopamine synthesis capacity, and choice and working memory performance

						coordinates		
Contrast	anatomical region	hemisphere	direction	t	corrected p	x	y	z
Proportion redo choices PBO	midbrain	right	negative	3.96	0.099	6	-36	-14
MPH effect on proportion redo choices	**midbrain**	**left**	**positive**	**4.73**	**0.013**	**-4**	**-32**	**-14**
	Pons	left	positive	3.86	0.124	-4	-38	-34
	nucleus accumbens	left	positive	3.68	0.185	-6	14	-6
	caudate nucleus	right	positive	3.47	0.283	20	6	14
	caudate nucleus	right	positive	3.32	0.373	16	-6	20
MPH vs SUL effect on proportion redo choices	midbrain	left	positive	3.55	0.254	-8	-30	-16
MPH effect on indifference point	**midbrain**	**left**	**positive**	**4.65**	**0.017**	**-4**	**-30**	**-16**
Choice latency PBO	**caudate nucleus**	**left**	**negative**	**4.44**	**0.029**	**-10**	**12**	**0**
	midbrain	**right**	**negative**	**4.27**	**0.045**	**4**	**-14**	**-12**
	midbrain	right	negative	4.11	0.068	4	-36	-14
	putamen	right	negative	3.46	0.287	32	-6	-4
	putamen	right	negative	3.45	0.290	20	18	-8
	amygdala	right	negative	3.34	0.357	28	-2	-14
MPH effect on choice latency	**putamen**	**right**	**positive**	**5.03**	**0.006**	**28**	**-8**	**0**
	caudate nucleus	**left**	**positive**	**4.94**	**0.007**	**-10**	**10**	**-4**
	midbrain	**left**	**positive**	**4.77**	**0.012**	**-4**	**-34**	**-18**
	midbrain	left	positive	3.51	0.258	-6	-8	-10
	medulla oblongata	right	positive	3.50	0.266	2	-42	-46
	caudate nucleus	left	positive	3.48	0.274	-18	-2	14
	nucleus accumbens	right	positive	3.39	0.326	4	12	-12
SUL effect on choice latency	caudate nucleus	left	positive	3.68	0.183	-10	8	-4
	caudate nucleus	right	positive	3.50	0.266	18	4	12
MPH vs SUL effect on choice latency	putamen	right	positive	3.59	0.236	28	0	0
	Pons	right	positive	3.41	0.334	6	-38	-24
	midbrain	right	positive	3.36	0.364	8	-32	-18
	amygdala	left	positive	3.34	0.380	-18	-6	-16
MPH effect on deviance (working memory task)	midbrain	right	positive	3.33	0.248	4	-38	-20
	caudate nucleus	left	positive	3.25	0.299	-12	6	2
	midbrain	right	positive	3.18	0.350	2	-36	-14
	caudate nucleus	left	positive	3.17	0.355	-18	0	16

Spatial coordinates of local maxima for regions showing a correlation with behavioral measures. Coordinates correspond to the standard MNI brain. Statistical interference was based on a peak-level correction of $p < 0.05$ (FWE) using small volume correction (a volume comprising all voxels with a Ki value of > 3 SD from the global mean). Caution is warranted: shown here, for full reporting, are all clusters with an uncorrected p-value < 0.001. Significant clusters are in bold.
PBO: placebo; MPH: methylphenidate; SUL: sulpiride. $N = 46$.

Methylphenidate increased indifference points

A priori we had planned to calculate indifference points (IPs): The offer for the no-redo option at which the participant was indifferent to either choosing no-redo or redoing the task for €2.00 (Figure S2.3A). However, because many participants demonstrated a very low willingness to redo the task, sometimes resulting in inestimable IPs, we instead decided to base our primary analyses on the proportion redo choices. A high IP means a strong preference for the cognitively more demanding redo option and high motivation for task engagement. The IP was calculated using binomial logistic regression analysis. Where IP was lower or higher than the minimum (€0.10) or maximum (€2.20) offer for the no-redo option, respectively, the IP was set to either 0.10 (in case of an IP lower than the minimum) or 2.20 (in case of an IP higher than the maximum), to avoid loss of valuable data. Table S2.7 shows the repeated-measures ANOVA results with the within-participants factors drug (methylphenidate, sulpiride, placebo), task-type (ignore, update) and set-size and the covariate dopamine synthesis capacity (separate analyses for the three ROIs – nucleus accumbens, putamen and caudate nucleus).

Under placebo, participants exhibited a strong preference for not repeating the task, as evidenced by the IP being significantly smaller than €2.00, the fixed offer for the redo option (0.79, SD = 0.55; *Cohen's d* = -2.19, 95% CI [-2.72, -1.65], $p < 0.001$).

In accordance with proportion redo choices, IP decreased with set-size ($\eta\eta_p^2 = 0.64$, 90% CI [0.55, 0.71], $p < 0.001$). There was no effect of task-type ($\eta_p^2 = 0.03$, 90% CI [0.00, 0.17], $p = 0.216$) and no interaction between task-type and set-size ($\eta_p^2 = 0.01$, 90% CI [0.00, 0.04], $p = 0.622$). We found a significant effect of drug on IP (main effect over the 3 drug conditions: $\eta_p^2 = 0.13$, 90% CI [0.03, 0.24], $p = 0.003$), which was driven by a positive effect of methylphenidate versus placebo ($\eta_p^2 = 0.17$, 90% CI [0.04, 0.35], $p = 0.004$; Figure S2.3B) and a positive effect of methylphenidate versus sulpiride ($\eta_p^2 = 0.16$, 90% CI [0.03, 0.34], $p = 0.005$). There was no difference between sulpiride and placebo ($\eta_p^2 = 0.00$, 90% CI [0.00, 0.07], $p = 0.780$; Figure S2.3B).

The interaction between drug effect on IP and dopamine synthesis capacity qualitatively resembled the interaction effect on proportion redo choices (nucleus accumbens: $\eta_p^2 = 0.07$, 90% CI [0.00, 0.17], $p = 0.036$; putamen: $\eta_p^2 = 0.07$, 90% CI [0.00, 0.16], $p = 0.044$; caudate nucleus: $\eta_p^2 = 0.05$, 90% CI [0.00, 0.13], $p = 0.112$; Table S2.7). Participants with higher dopamine synthesis capacity in the nucleus accumbens exhibited greater methylphenidate-induced increases in IP than participants with lower dopamine synthesis capacity ($\eta_p^2 = 0.11$, 90% CI [0.01, 0.28], $p = 0.022$). A negative association between dopamine synthesis capacity and IP under placebo was not significant (Table S2.7).

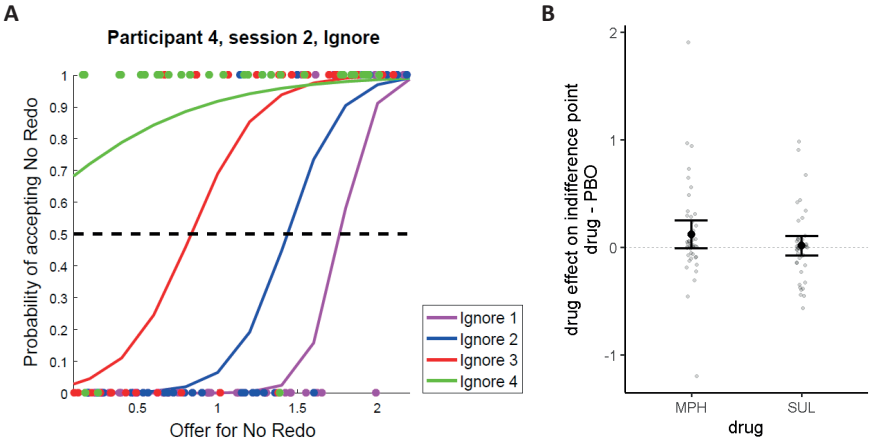

FIGURE S2.3 | Indifference point. **A** – Probability of choosing the no-redo option as a function of the monetary offer for the no-redo option on Ignore trials during session 2 for a representative participant. Fitted probability functions for each set-size are plotted using logistic regression. The indifference point (IP) – where the probability line hits the dashed line – is the offer for the no-redo option at which there is a 50% chance that the participant chose no-redo for that amount or redo for €2. **B** – Drug effect on indifference point (methylphenidate or sulpiride minus placebo). Error bars represent 95% confidence interval around the mean. MPH: methylphenidate; SUL: sulpiride; PBO: placebo.

TABLE S2.7 | Repeated-measures ANOVAs on indifference points. Separate analysis for each ROI – nucleus accumbens, putamen and caudate nucleus, including drug, set-size and task-type as within-subjects variables and dopamine synthesis capacity (measured as the mean-centered average [^{18}F]DOPA uptake, K_i) as covariate. Partial eta squared (η_p^2), 90% confidence intervals around η_p^2 and *p*-values for the interaction between dopamine synthesis and drug are shown, as well as the main effect of dopamine synthesis capacity on the placebo session. MPH = methylphenidate; SUL = sulpiride; PBO = placebo.

	Nucleus accumbens		Putamen		Caudate nucleus	
	η_p^2	*p*	η_p^2	*p*	η_p^2	*p*
MPH, SUL, PBO	0.07 [0.00, 0.17]	0.036	0.07 [0.00, 0.16]	0.044	0.05 [0.00, 0.13]	0.112
post-hoc:						
MPH, PBO	0.11 [0.01, 0.28]	0.022	0.11 [0.01, 0.28]	0.025	0.08 [0.00, 0.24]	0.054
SUL, PBO	0.01 [0.00, 0.11]	0.502	0.01 [0.00, 0.12]	0.451	0.04 [0.00, 0.17]	0.198
MPH, SUL	0.07 [0.00, 0.23]	0.067	0.06 [0.00, 0.22]	0.088	0.02 [0.00, 0.13]	0.366
PBO	0.08 [0.00, 0.24]	0.058	0.03 [0.00, 0.17]	0.221	0.01 [0.00, 0.09]	0.619

Methylphenidate-induced effect does not reflect choice randomness

Choice randomness would be evidenced by the proportion redo choices being close to 0.5. It is possible that methylphenidate increased choice randomness rather than cognitive motivation for high-dopamine individuals, resulting in a higher proportion redo choice. We therefore explored the choice slopes (see also Figure S2.3A). If participants were more random in their choices, their slope should be shallower. Two persons had an overall slope that was higher than three standard deviations above the global mean and were therefore excluded. Moreover, the slope could not be estimated if a participant's IP was outside the sampled range (€0.10-€2.20). Because this was the case for most participants when calculating the slope separately for each combination of the three factors (drug, task-type and set-size), we assessed slope only as a function of drug (with conditions methylphenidate and placebo) to maximize the number of participants that could be included: N = 32. A rmANOVA revealed no effect of drug (η_p^2 = 0.07, 90% CI [0.00, 0.26], p = 0.150) nor an interaction between dopamine synthesis capacity and drug (nucleus accumbens: η_p^2 = 0.00, 90% CI [0.00, 0.11], p = 0.710; putamen: η_p^2 = 0.00, 90% CI [0.00, 0.05], p = 0.880; caudate nucleus: η_p^2 = 0.00, 90% CI [0.00, 1.00], p = 0.997). We thus conclude that the dopamine synthesis capacity-dependent effect of methylphenidate on motivation did not reflect an effect on choice randomness.

Dopamine synthesis capacity-dependent effects cannot be explained by working-memory performance

Although drugs were only administered after the working-memory task, we aimed to confirm that effects on performance could not explain the dopamine synthesis capacity-dependent effects of methylphenidate. We therefore ran the rmANOVAs again for deviance and RT, including the within-subjects variables task-type, set-size and drug and the covariate dopamine synthesis capacity. There were no main effects of drug on deviance (η_p^2 = 0.03, 90% CI [0.00, 0.09], p = 0.306) or RT (η_p^2 = 0.02, 90% CI [0.00, 0.07], p = 0.451) and no interactions between dopamine synthesis capacity and drugs on deviance (nucleus accumbens: η_p^2 = 0.04, 90% CI [0.00, 0.12], p = 0.152; putamen: η_p^2 = 0.06, 90% CI [0.00, 0.15], p = 0.071; caudate nucleus: η_p^2 = 0.03, 90% CI [0.00, 0.10], p = 0.258) or RT (nucleus accumbens: η_p^2 = 0.00, 90% CI [0.00, 1.00], p = 0.995; putamen: η_p^2 = 0.01, 90% CI [0.00, 0.06], p = 0.615; caudate nucleus: η_p^2 = 0.00, 90% CI [0.00, 1.00], p = 0.987). No other interactions including drug or dopamine synthesis capacity were significant.

We also assessed a potential association between methylphenidate-related changes in performance and proportion redo choices or choice latency with a Pearson's correlation.

As expected, the effect of methylphenidate on performance did not correlate with the effect of methylphenidate on proportion redo choices (deviance: r = 0.10, 95% CI [-0.19, 0.38], p = 0.493; RT: r = 0.16, 95% CI [-0.13, 0.43], p = 0.276) or choice latency (deviance: r = 0.16, 95% CI [-0.14, 0.43], p = 0.297; RT: r = 0.14, 95% CI [-0.16, 0.42], p = 0.347). It is therefore unlikely that methylphenidate-effects on choice behavior can be explained by changes in performance.

Dopamine-dependent effects cannot be explained by mood and medical symptoms

On the pharmacological sessions (day 2-4), blood pressure, heart rate and ear temperature were monitored three times on each session: before the start of the task battery, 20 minutes before the start of the discounting task and after the task battery. At the same timepoints, mood measures (Positive and Negative Affect Scale (Watson et al., 1988); the Bond and Lader Visual Analogue Scales (calmness, contentedness, alertness; (Bond & Lader, 1974))) and medical symptoms (medical visual analogue scale) were assessed. Table S2.5 gives an overview of those measures for the participants included in the analyses.

To assess whether methylphenidate-induced effects could be accounted for by nonspecific effects of methylphenidate on mood and medical symptoms, we performed a repeated measures MANOVA in SPSS (IBM SPSS statistics version 23.0) using Pillai's trace with the within-subject factors Time (3: before the start of the task battery, 20 minutes after intake of the second capsule and after the task battery) and Drug (3: placebo, methylphenidate and sulpiride) and the six measures as dependent variables (positive affect, negative affect, calmness, alertness, contentedness, medical symptoms). Significant initial MANOVA results (p < 0.05) were followed up with univariate tests of the interaction effect (drug x time) for each of the six dependent variables, with Bonferroni-corrected alpha = 0.05/6 ≈ 0.008.

Drug did not significantly affect the mood and medical measures over time (drug x time: V = 0.68, η_p^2 = 0.64, p = 0.057). We conducted the MANOVA again, but now with only the first two timepoints, given the proximity of the second timepoint to the choice task (20 minutes before the start of the task). This revealed a significant drug effect over time (drug x time: V = 0.48, η_p^2 = 0.48, p = 0.015). However, none of the univariate interactions between drug and time for the six dependent variables was significant (all η_p^2 < 0.60, p > 0.061). A MANOVA on only timepoint 2 revealed no significant effect of drug (V = 0.38, η_p^2 = 0.38, p = 0.107).

Next, we correlated methylphenidate-induced changes on the six mood and medical measures at timepoint 2 with methylphenidate-induced changes in proportion redo choices. This revealed a positive correlation for positive affect (r = 0.34, 95% CI [0.05, 0.57], p = 0.022) and alertness (r = 0.28, 95% CI [-0.01, 0.53], p = 0.060). The other correlations were all below r = 0.16 and above p = 0.283. We therefore ran additional repeated-measures ANOVAs on proportion redo choices with drug (methylphenidate and placebo), task-type (ignore and update) and set-size as within-subjects variables and dopamine synthesis capacity as a covariate, while also including the effect of methylphenidate on positive affect and alertness, respectively, as a covariate. Methylphenidate still significantly affected proportion redo choices when including positive affect, both as a main effect (η_p^2 = 0.17, 90% CI [0.03, 0.36], p = 0.004) and in interaction with dopamine synthesis capacity (nucleus accumbens: η_p^2 = 0.18, 90% CI [0.04, 0.36], p = 0.013; putamen: η_p^2 = 0.20, 90% CI [0.02, 0.33], p = 0.008; caudate nucleus: η_p^2 = 0.11, 90% CI [0.01, 0.28], p = 0.024). Similarly, methylphenidate still significantly affected proportion redo choices when including alertness, both as a main effect (η_p^2 = 0.18, 90% CI [0.04, 0.36], p = 0.004) and in interaction with dopamine synthesis capacity (nucleus accumbens: η_p^2 = 0.21, 90% CI [0.05, 0.39], p = 0.002; putamen: η_p^2 = 0.20, 90% CI [0.05, 0.39], p = 0.002; caudate nucleus: η_p^2 = 0.15, 90% CI [0.03, 0.34], p = 0.008). It is therefore unlikely that drug-induced changes on mood or medical measures account for effects on proportion redo choices.

Controlling for session order

High-dopamine individuals received methylphenidate on earlier sessions than low-dopamine individuals

A first ANOVA confirmed that session-day-number (1, 2 or 3) did not differ between the three drugs (η_p^2= 0.01, 90% CI [0.00, 0.05], p = 0.420). The order of the drug session could further potentially have confounded our dopamine synthesis capacity-dependency effects if people with lower dopamine synthesis capacity accidentally experienced a different order than people with higher synthesis capacity. Unexpectedly, a Spearman's rank correlation indeed revealed that dopamine synthesis capacity was negatively correlated with the session on which participants received methylphenidate (Table S2.8). Participants with higher dopamine synthesis capacity more often received methylphenidate on the earlier sessions. There were no significant correlations between dopamine synthesis capacity and the session on which participants received sulpiride or placebo (Table S2.8). Given these findings, we reanalyzed our significant methylphenidate effects and methylphenidate by dopamine synthesis capacity interactions while controlling for the methylphenidate session number by adding methylphenidate's session number as a between-subjects factor to the rmANOVA.

Table S2.8 | Spearman's rank correlations between dopamine synthesis capacity and session number on which participants received methylphenidate, sulpiride and placebo.

	Nucleus accumbens		Putamen		Caudate nucleus	
	rho	*p*	*rho*	*p*	*rho*	*p*
Methylphenidate	-0.29	0.047	-0.40	0.005	-0.24	0.116
Sulpiride	0.11	0.481	0.24	0.107	0.11	0.453
Placebo	0.22	0.145	0.21	0.167	0.15	0.310

After including methylphenidate's session number as a between-subjects factor, methylphenidate, relative to placebo, still significantly increased proportion redo choices (η_p^2 = 0.14, 90% CI [0.02, 0.32], p = 0.012). The interaction effects between dopamine synthesis capacity and methylphenidate on proportion redo choices and choice latency were also the same as those reported in the main manuscript (proportion redo choices: nucleus accumbens: η_p^2 = 0.10, 90% CI [0.00, 0.27], p = 0.038; putamen: η_p^2 = 0.05, 90% CI [0.00, 0.21], p = 0.127; caudate nucleus: η_p^2 = 0.09, 90% CI [0.00, 0.25], p = 0.051; choice latency: nucleus accumbens: η_p^2 = 0.11, 90% CI [0.01, 0.29], p = 0.026; putamen: η_p^2 = 0.08, 90% CI [0.00, 0.24], p = 0.071; caudate nucleus: η_p^2 = 0.03, 90% CI [0.00, 0.16], p = 0.252).

No correlation between dopamine synthesis capacity and time after methylphenidate administration

Previous research suggested that increased striatal dopamine synthesis capacity can be detected by an [^{18}F]DOPA scan in conjunction with the inlet–outlet model even 2 weeks after a methylphenidate treatment (Schabram et al., 2014). We therefore assessed whether the order effects could have arisen due to too short intervals between the drug sessions and the PET scan. The interval between the methylphenidate session and the PET scan ranged between 7 and 106 days (mean = 43.0, SD = 26.8). However, Pearson's correlations between dopamine synthesis capacity and days between the methylphenidate session and the PET scan were not significant (nucleus accumbens: r = 0.16, 95% CI [-0.14, 0.43], p = 0.303; putamen: r = 0.18, 95% CI [-0.12, 0.44], p = 0.245; caudate nucleus: r = 0.04, 95% CI [-0.26, 0.33], p = 0.786), thus minimizing the likelihood that our index of dopamine synthesis capacity was affected by drug administration.

Drug effects on physiological measures

Primary analyses revealed no significant effects of sulpiride. To assess whether this could be explained by a general lack of sulpiride effect, we performed a repeated

measures MANOVA on the physiological measures heart rate, systolic blood pressure, diastolic blood pressure and ear temperature. The within-subject factors were Time (3: before the start of the task battery, 20 before the start of the discounting task and after the task battery) and Drug (3: placebo, methylphenidate and sulpiride). Significant effects were followed up with univariate tests of the interaction effect (drug x time) for each of the four dependent variables, with Bonferroni-corrected alpha = 0.05/4 ≈ 0.013.

Drug significantly affected heart rate and blood pressure over time (drug x time: V = 0.73, η_p^2 = 0.73, p < 0.001; heart rate: η_p^2 = 0.25, p < 0.001; systolic blood pressure: η_p^2 = 0.13, p < 0.001; diastolic blood pressure: η_p^2 = 0.13, p < 0.001), but not ear temperature (η_p^2 = 0.06, p = 0.035). The effect was driven by a difference between methylphenidate and placebo (V = 0.65, η_p^2 = 0.65, p < 0.001). Over time, methylphenidate increased heart rate (η_p^2 = 0.32, p < 0.001), systolic blood pressure (η_p^2 = 0.14, p = 0.001) and diastolic blood pressure (η_p^2 = 0.17, p < 0.001) compared with placebo. There were no significant effects of sulpiride over time (V = 0.14, η_p^2 = 0.14, p = 0.654). We conducted the MANOVA again, but now with only the first two timepoints, given the proximity of the second timepoint to the choice task (20 minutes before the start of the task). This revealed no significant drug effect over time (drug x time: V = 0.18, η_p^2 = 0.19, p = 0.426). A MANOVA on only timepoint 2 revealed a significant effect of drug (V = 0.44, η_p^2 = 0.44, p = 0.003). However, only the univariate analysis on diastolic blood pressure revealed an effect of drug that did not reach significance after correction for multiple comparisons (η_p^2 = 0.08, p = 0.023). The drug effects on the other dependent variables were all below η_p^2 = 0.04 and above p = 0.145. This non-significant effect on diastolic blood pressure stemmed from a difference between methylphenidate and sulpiride (η_p^2 = 0.14, p = 0.011), where diastolic blood pressure was higher on the methylphenidate session. Thus, although there were clear physiological effects of methylphenidate over time, these only emerged when including the third timepoint. There were no clear physiological effects of sulpiride.

Supplemental discussion

Cognitive stability versus cognitive flexibility

In addition to investigating choices between cognitive control and rest, we assessed choices between different types of cognitive control. Specifically, we were interested to explore catecholaminergic drug effects on choices between a working memory "update" task requiring cognitive flexibility and a working memory "ignore" task requiring cognitive stability (Cools & D'Esposito, 2011; Fallon et al., 2017; Musslick

et al., 2018). Our data showed no strong evidence for methylphenidate or sulpiride shifting the balance between the motivation for stable versus flexible control. This might be not surprising, because, contrary to earlier studies, in which participants preferred a similar flexible update task over a stable ignore task (Froböse et al., 2018; Papadopetraki et al., 2019), there was no difference between the value of the two tasks under placebo. It is potentially relevant that here, in contrast to that previous work, participants did not choose between the "update" or "ignore" task, but rather between one of those tasks and a rest option. For future work, to investigate the question whether dopamine alters preference for one task versus another, we would require direct choices between the two types of task, while also considering the manipulation across time of the frequency of one task-type over another.

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CHAPTER 3

Does incentive motivation boost cognitive meta-control?

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Abstract

Working memory involves the dynamic balance between the stable maintenance and the flexible updating of goal representations. In an environment with high demands for flexible updating, it is adaptive to weaken task-representations in order to update goal representations more easily, whereas in an environment with high demands for goal maintenance, it is more adaptive to strengthen task representations. It has been argued that such strategic meta-control, which depends on preparatory processes, is particularly recruited when incentive motivation is high. Here, we tested whether incentive motivation potentiates strategic meta-control using a delayed working memory paradigm that distinguishes between two different trial-types, one demanding flexible update and the other demanding stability. We manipulated the extent to which participants could exert strategic meta-control by varying the frequency of one trial-type over the other, allowing participants to prepare for the high-frequent trial type. We expected participants to be better prepared for demands for flexibility or stability when either is, respectively, more frequent, and that greater incentive motivation would strengthen this effect. While we did not find evidence for the predicted effects of incentive motivation on strategic meta-control in terms of accuracy, exploratory reaction time analyses showed greater slowing on update trials when this was the high-frequent trial-type. Future studies with larger trial numbers might leverage reaction time distributions to investigate the hypothesis that this effect reflects a strategically controlled increase in a decision threshold.

Introduction

Cognitive control is generally referred to as a set of mechanisms required for goal-directed behavior, involving preparation and maintenance of rules to bias action and attention in working memory (Egner, 2017; Fuster, 1989; Monsell, 2003). A key aspect is to maintain stable goal representations, even in the face of distraction. However, such cognitive stability may incur a cost if the current goal becomes less beneficial relative to other potential goals. Thus, another essential feature of cognitive control is the ability to flexibly switch between goals when needed. This means that constantly a balance is sought between a stable focus on the current task and a flexible readiness to attend to new incoming stimuli, potentially associated with other rewards. Balancing this tradeoff requires a form of meta-level strategic control to incorporate task-relevant information, such as the required cognitive load or the potential costs and benefits of completing the task that in turn often depend on the contextual demands for stability versus flexibility (Boureau et al., 2015; Cools, 2019; Goschke & Bolte, 2014; Musslick et al., 2018). Here, we investigate the degree to which incentives and contextual demands for flexibility versus stability contribute to biasing people towards flexibility versus stability.

In a stable environment where goals do not change much, we can strongly focus on current goal representations without the need to regularly destabilize them. However, when the demands for flexible updating are high, we must regularly let go of previous goal representations, and destabilize them to replace them with new goal representations. In neural network simulations of the flexibility / stability tradeoff (Musslick et al., 2018), the cost of stable, focused control indexes demands for flexibility. In environments demanding flexibility, treating stability as more costly thus motivates weaker, more flexible goal representations, which increase flexibility while also diminishing controlled focus. Conversely, a context with high demands for stable maintenance will benefit from a strengthening of current goal representations. Support for this observation was obtained from neural network simulations of performance on a task-switching paradigm with Stroop targets. These demonstrated that stability costs, indexed by Stroop interference scores, were higher when the frequency of task-switches was high. The implication of this observation is that people can proactively alter the strength of their current goal activation depending on the demands for flexibility of the environment.

It has been argued that preparatory meta-control – of the sort needed to prepare for expected environmental demands – is particularly recruited when motivational incentives are high. By one proposal, motivational incentives would improve the neural signal-to-noise ratio in the frontal cortex via dopaminergic signaling, thereby

sharpening task representations (Braver, 2012; Braver et al., 2014; Yee & Braver, 2018). Chiew and Braver have indeed shown that monetary incentives improved cognitive performance by increasing control (Chiew & Braver, 2016). Incentives reduced Flanker interference costs, with a greater effect when a cue indicated whether or not the Flanker stimuli would be congruent, allowing them to proactively prepare for the trial. In line with these behavioral findings and consistent with the hypothesis that motivation sharpens neural task representations, another study showed improved task set representation in frontoparietal brain regions when participants saw a cue indicating that they could win a reward on that trial (Etzel et al., 2016). Specifically, participants performed a cued task switching paradigm in which they had to respond to either the face or the word of an overlapping face/word stimulus. Decoding-accuracy of task-specific voxel-level BOLD activity patterns (for a face or word task) was better on high reward than on low reward incentive trials. Critically, this neural effect was associated with an incentive-related increase in behavioral performance accuracy.

Grounded in these earlier studies on the effect of motivation on preparatory control, we here test whether incentive motivation affects meta-regulation of the flexibility/stability tradeoff in an adapted version of the delayed working memory paradigm (Papadopetraki et al., 2019; Prinzmetal et al., 1997; Wilken & Ma, 2004). In addition, we bias participants to prepare for either stable or flexible working memory demands in the upcoming trial: in one context there is an equal frequency of both trial-types. In other contexts, the frequency of one task is higher than that of the other task, allowing for preparation for the high-frequent trial-type. Incentive motivation is manipulated in a trial-wise fashion by incentive magnitude. We predicted that participants would exhibit meta-level control and thus perform better on a task when it is highly frequent, with higher incentive motivation strengthening this effect.

Methods

Participants

Thirty-five healthy and right-handed participants were recruited via SONA, the research participation system of the Radboud University. The procedure of this study was approved by the local ethics committee (CMO region Arnhem-Nijmegen, The Netherlands; protocol 2014/288 version 1.4). Before the start of the experiment, participants gave written consent. Participants were paid 8 euro per hour plus a bonus contingent on their performance, ranging between 3.58 and 7.10 euro. One participant was excluded from data analysis (see below), resulting in 34 participants (24 women; age: mean (SD) = 24.7 (3.2), range 19 – 33).

Procedure

The experiment was performed on a computer running on Windows 7 with a screen resolution of 1920x1080p and a grey background color (R:200 G:200 B:200). The task was programmed in MATLAB version 2017a, using Psychophysics Toolbox Version 3.0.12.

Color sensitivity task

Participants first completed a color sensitivity task measuring the ability to detect and distinguish the colors in the main experiment. This task consisted of 12 trials where participants had to match the color of a square in the center of a color wheel to the corresponding color on the wheel, by moving the mouse toward the wheel. Once they reached a color on the wheel, that color was taken as their response. If the average deviation of the response from the true color was more than 15 degrees, the task was assessed again. Participants would be excluded after a second failure.

The color wheel was created with the HSV MATLAB color map and was divided into 12 parts, each from which one color was randomly chosen to be the target color. The orientation of the color wheel was randomized across trials. After each trial, a first black line confirmed the response and a second line indicated the true color. Additional feedback conveying the absolute number of degrees to which the response deviated from the true color (deviance) was given if the deviance was below 10 degrees: e.g. 'Good job! You deviated only 4 degrees!'. Participants were instructed to answer precisely, but not to take too much time to respond. There was no maximum response time, but participants were instructed to first determine their response and only then move their mouse as fast as possible toward the wheel.

Color wheel working memory task

In the color wheel task, participants viewed an array of colors and, after a delay, reported the color of one probed item from the array. A visual representation is depicted in Figure 3.1. On each trial, an incentive cue ranging from 5 to 95 points was presented on screen. This incentive cue varied as a function of a Gaussian random walk with a standard deviation of 20. These parameters were chosen to optimize measurement of the effect of fluctuating average reward rates (averaged across a history of recent trials), motivated by a question about a possible effect of average reward (or opportunity cost) on meta-control (Otto & Daw, 2019). However, addressing this question is outside the scope of the current thesis. After 750ms participants were instructed to press the space bar to start the trial. After a blank screen lasting 500ms,

three colored items were presented in the middle of the screen, with the letter 'M' for 'memorize' in the middle. During this encoding phase, participants had 500ms to memorize the colors of the items, after which there was a delay of 500ms during which a fixation cross was shown. A new set of colored items then appeared on screen, with one of two letters in the center. 'I' for 'ignore': participants had to ignore the new items while still remembering the old set of items; 'U' or 'update': participants now had to memorize the new set of items and forget the old items. This interference phase lasted 500ms and was followed by a second delay phase. Dependent on the trial-type, ignore or update, this delay lasted either 500ms or 1500ms, respectively, in order to match the time interval between the relevant items (the first set for ignore and the second set for update) and the probe phase. During this probe phase, the color wheel appeared on the screen together with one outlined frame that indicated the location of the item that should be reported. Participants had up to 4000ms to decide on their response before moving the mouse toward their desired color. Once they started moving the mouse, they had a short time window to reach the color wheel, which was individually determined by their median time to move the mouse toward the wheel during the color sensitivity task. Every tenth trial, this deadline was shortened with 100ms to promote fast responding (Beierholm et al., 2013; Guitart-Masip et al., 2011; Otto & Daw, 2019). The distinction between time to determine their response and time to move the mouse was made to minimize the contribution of motor processes to reaction times. However, the time to reach the color wheel was very short compared with the time to determine the response and our primary analyses revealed equivalent results for total response time and time to determine a response. We therefore only report total response time (RT), which was calculated as the sum over the time it took the participant to determine their response and the time it took to reach the color wheel.

The task was preceded by two practice blocks of 8 trials each. The first block was without incentives to familiarize participants with the difference between the ignore and update trial-types. Feedback was provided as a second line indicating the true color. During the second practice block the trials were preceded by an incentive cue. No line indicating the true color was presented, but participants received feedback about their received reward, which was equal to the number of points indicated at the start of the trial when their deviance fell within 15 degrees or zero otherwise.

During the actual task, participants received the reward if their response was considered correct, i.e., fell within an individually set response window, determined separately for ignore and update trials as the 85th percentile deviance score across all practice trials of that trial-type. Participants were instructed that they would earn a monetary bonus proportional to the total received reward during the task.

Participants completed three blocks of the color wheel task, each lasting 12 minutes. On average, participants completed 98 trials per block (SD = 6, range = 76 – 108). It is of note here that participants could win more reward the more trials they completed (while maintaining their accuracy) within those 12 minutes, which was also explicitly communicated to the participants. Thus, both accuracy and speed were important in this paradigm. In the first block, the trials were equally divided between ignore and update (neutral context), where the demand for proactive control was minimal. To bias meta-control processes we manipulated the frequency of the trial-types in two additional blocks, counterbalanced across participants, with one block consisting of 67% ignore trial-type and 33% update trial-type (majority ignore context) and the other block consisting of 67% update trial-type and 33% ignore trial-type (majority update context). The participants were explicitly informed about these contexts during the instruction phase and again at the start of each block by "You will get mostly IGNORE/ UPDATE" being shown on the screen, after which they had to press the space bar. The colors that were presented during the encoding phase of ignore trials were matched to the colors that were presented during the interference phase of update trials and vice versa. The target colors were the same for both trial-types and the location of the target item was balanced across trial-types. Participants experienced the same set of stimuli in each context, but in randomized order. The orientation of the color wheel was randomized across trials.

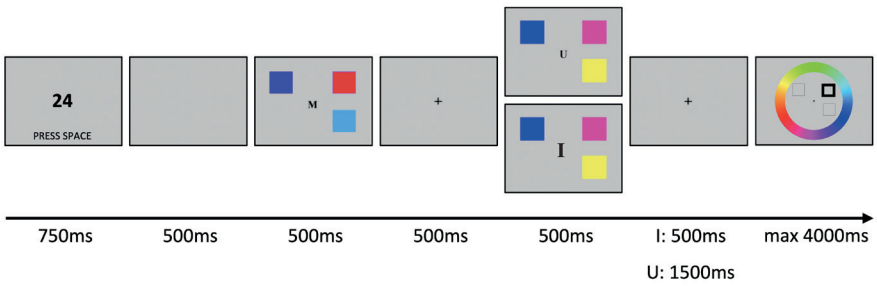

FIGURE 3.1 | Schematic of the color wheel working memory task where participants have to indicate the color of an outlined target item on the color wheel. M = memorize: participants had to memorize the colors of the items. I = ignore trial-type: participants have to ignore the new items while still remembering the previous items. U = update trial-type: participants have to remember the new items and forget the previous items. The number of points at the start of the trial in indicates the number of points to be earned if performance on that trial is below an individually set threshold.

Data analysis

Our primary dependent variables were deviance and response time, but we also explored whether the participant received a reward or not: the proportion of correct trials. Outliers were defined a priori as participants whose mean overall deviance

was either more than 3 standard deviations higher than that of the global mean, which resulted in one exclusion. We analyzed our data in R version 3.4.2 (R Core Team, 2018) using a combination of primary Bayesian trial-by-trial mixed effects modeling supplemented by repeated-measures ANOVAs (rmANOVAs) on summary data to confirm the results and to accommodate readers who are used to interpreting frequentist statistics.

The Bayesian mixed effects models were performed using the brm function from the brms package (Bürkner, 2017). These models allowed for a trial-wise analysis and for incentive to be modeled as a continuous variable. We analyzed deviance, RT and whether participants received a reward on that trial (trials correct). The family functions used were lognormal for deviance and RT, and Bernoulli for trials correct. The omnibus model included the main effects of the predictors incentive (continuous), trial-type (ignore, update) and context (majority ignore, majority update, neutral) and their interactions as fixed effects, and random intercepts and slopes per participant for the same effects. To improve model performance and interpretability, incentive was z-scored and the categorical variables were coded as sum-to-zero contrasts. The contrasts for the context factor were represented as 1) ignore versus the grand mean of all contexts and 2) update versus the grand mean of all contexts. We used default brms-priors. The model was fit using four chains with 10,000 iterations each (5,000 warm-up) and were inspected for convergence. Coefficients were considered statistically significant if the 95% posterior credible intervals did not overlap with zero.

The omnibus model represents three levels of the context factor and interpretation of effects including this factor is complicated. Therefore, we additionally ran pairwise comparisons contrasting each pair of contexts. Upon significant interactions that included the factor context, we ran separate models for each context. These follow-up models were otherwise computed as described above.

The rmANOVAs were performed on mean deviance, mean RT and the proportion of trials on which participants received a reward (proportion correct) and included the within-subjects factors incentive (median split per individual: low, high), trial-type (ignore, update) and context (majority ignore, majority update, neutral). The analyses were performed using the ezANOVA function from the ez package (Lawrence, 2016). When the assumption of sphericity was violated, we report Greenhouse-Geisser corrected *p*-values. If an interaction was significant, we followed-up with post-hoc tests contrasting each pair of contexts (majority ignore versus majority update; majority ignore versus neutral; majority update versus neutral) and assessing the effects of incentive and trial-type separately for each context.

Additionally, we ran a repeated measures correlation to assess a potential speed-accuracy trade-off between deviance and response time using the rmcorr package in R (Bakdash & Marusich, 2018).

To assess potential effects of meta-control or incentive on distributional skew (De Jong, 2000; Nieuwenhuis & Monsel, 2002), we performed ex-Gaussian analyses. The analyses were performed using the mexgauss function from the retimes package in R (Massidda, 2013) to calculate central tendency (μ and σ parameters) and skew (τ parameter) for each context, trial-type and incentive (low, high) for each participant, followed by a rmANOVA with the within-subjects factors context, trial-type and incentive. We briefly report the results below for the purpose of full reporting. However, given the low number of trials per condition we deemed our statistical power low (range = 5-51) (Heathcote et al., 2004) and warrant caution in interpreting these results.

Results

Better performance on update than ignore trials

In line with previous studies using this paradigm (Hofmans et al., 2020; Papadopetraki et al., 2019), participants were less accurate on ignore trials than on update trials, both in terms of deviance (**BRMS**: 95% CI = [0.21, 0.31]; **rmANOVA**: $F_{(1,33)} = 124.0$, $p = 1.02e^{-12}$; Figure 3.2A) and trials correct (**BRMS**: 95% CI = [-0.62, -0.06]; **rmANOVA**: $F_{(1,33)} = 5.2$, $p = 0.029$; Figure 3.2B). Additionally, as in previous studies, they were faster on ignore trials than on update trials (**BRMS**: 95% CI = [-0.05, -0.02]; **rmANOVA**: $F_{(1,33)} = 23.3$, $p = 3.11e^{-5}$; Figure 3.2C).

Does context elicit meta-level strategy prioritization?

We then assessed whether we succeeded in isolating a meta-control effect using this paradigm. Such an effect of meta-control would be evident in terms of an interaction between trial-type and context, with better performance on ignore trials in a block where the majority of trials were ignore trials and better performance on update trials in a block where the majority of trials were update trials. This interaction was not significant for either deviance (**BRMS**: 95% CI *majority ignore versus neutral* = [-0.03, 0.05], *majority update versus neutral* = [-0.03, 0.04], *majority ignore versus majority update* = [-0.03, 0.05]; **rmANOVA**: $F_{(2,66)} = 1.6$, $p = 0.219$; Figure 3.2A) or trials correct (trials on which reward was received; **BRMS**: 95% CI *majority ignore versus neutral* = [-0.12, 0.11], *majority update versus neutral* = [-0.13, 0.07], *majority ignore versus majority update* = [-0.10, 0.15]; **rmANOVA**: $F_{(2,66)} = 1.2$, $p = 0.322$; Figure 3.2B). Thus, there

was no evidence from accuracy data that participants used the context information to prioritize strategy and thus enhance performance. However, we did see a significant interaction between trial-type and context on RT (**rmANOVA**: *omnibus*: $F_{(2,66)}$ = 4.0, p = 0.024; Figure 3.2C), which was driven by a difference in the effect of trial-type between the majority ignore and majority update context (Trial-type x context: **BRMS**: 95% CI = [0.01, 0.02]; **rmANOVA**: $F_{(1,33)}$ = 8.0, p = 0.008). This was due to participants being slower on update trials than on ignore trials to a larger degree in the majority update context (**BRMS**: 95% CI = [-0.07, -0.03]; **rmANOVA**: $F_{(1,33)}$ = 20.2, p = 8.14e^{-5}) than in the majority ignore context (**BRMS**: 95% CI = [-0.05, -0.00]; **rmANOVA**: $F_{(1,33)}$ = 3.7, p = 0.065). The interaction between trial-type and context was not significant when comparing the neutral context with either the majority ignore (**BRMS**: 95% CI = [-0.00, 0.02]; **rmANOVA**: $F_{(1,33)}$ = 3.7, p = 0.064) or the majority update context (**BRMS**: 95% CI = [-0.01, 0.00]; **rmANOVA**: $F_{(1,33}$) = 0.7, p = 0.420).

Context biases performance nonselectively

Analyses of deviance revealed a significant main effect of context (**rmANOVA**: $F_{(2,66)}$ = 5.7, p = 0.005; Figure 3.2A), indicating lower deviance in the majority ignore versus both the neutral context (**BRMS**: 95% CI = [-0.12, -0.03]; **rmANOVA**: $F_{(1,33)}$ = 10.6, p = 0.003) and the majority update context (**BRMS**: 95% CI = [-0.09, -0.01]; **rmANOVA**: $F_{(1,33)}$ = 6.8, p = 0.013). There was no difference between the majority update and the neutral context (**BRMS**: 95% CI = [-0.06, 0.02]; **rmANOVA**: $F_{(1,33)}$ = 0.2, p = 0.667). The effect of context was similar for trials correct (**rmANOVA**: $F_{(2,66)}$ = 7.1, p = 0.002; Figure 3.2B), with participants being more often correct in the majority ignore versus both the neutral context (**BRMS**: 95% CI = [0.08, 0.33]; **rmANOVA**: $F_{(1,33)}$ = 11.7, p = 0.002) and the majority update context (**BRMS**: 95% CI = [0.04, 0.28]; **rmANOVA**: $F_{(1,33)}$ = 9.5, p = 0.004). Again, there was no difference between the majority update and the neutral context (**BRMS**: 95% CI = [-0.06, 0.14]; **rmANOVA**: $F_{(1,33)}$ = 0.3, p = 0.612). The observation that participants performed better in the majority ignore context might represent a different, unpredicted form of meta-control, where the more demanding and stability-requiring majority ignore context improves performance nonselectively, independent of trial-type.

We additionally observed a significant main effect of context on RT (**rmANOVA**: $F_{(2,66)}$ = 28.7, p = 7.10e^{-8}; Figure 3.2C), with participants being faster in the majority update versus the neutral context (**BRMS**: 95% CI = [-0.08, -0.04]; **rmANOVA**: $F_{(1,33)}$ = 33.0, p = 2.04e^{-6}) and in the majority ignore versus the neutral context (**BRMS**: 95% CI = [-0.10, -0.04]; **rmANOVA**: $F_{(1,33)}$ = 34.2, p = 1.52e^{-6}), potentially owing to practice effects due to the order of the contexts, as the neural context was always the first block. There was no difference between the majority ignore and majority update context (**BRMS**: 95% CI = [-0.01, 0.02]; **rmANOVA**: $F_{(1,33)}$ = 0.06, p = 0.808).

Does incentive motivation facilitate meta-control?

We considered the possibility that an effect of meta-control might depend on the degree to which participants were motivated. Thus, next we assessed whether an effect of meta-control, that is the interaction between context and trial-type or the main effect of context, varied as a function of incentive motivation.

Contrary to our hypothesis, analyses of deviance revealed no interaction between incentive, trial-type and context (**BRMS**: 95% CI *majority ignore versus neutral* = [-0.02, 0.05], *majority update versus neutral* = [-0.04, 0.03], *majority ignore versus majority update* = [-0.02, 0.06]; **rmANOVA**: $F_{(2,66)}$ = 1.4, p = 0.257; Figure 3.3A). Similarly, we did not observe a significant interaction between incentive, trial-type and context for trials correct (**BRMS**: 95% CI *majority ignore versus neutral* = [-0.14, 0.09], *majority update versus neutral* = [-0.13, 0.08], *majority ignore versus majority update* = [-0.12, 0.12]; **rmANOVA**: $F_{(2,66)}$ = 2.0, p = 0.156; Figure 3.3B).

However, analyses of RT did reveal an interaction between incentive, trial-type and context for the comparison between the majority update versus the neutral context (**BRMS**: 95% CI *majority update versus neutral* = [-0.02, -0.00], *majority ignore versus neutral* = [-0.01, 0.00], *majority ignore versus majority update* = [-0.00, 0.01]; **rmANOVA**: *omnibus*: $F_{(2,66)}$ = 2.7, p = 0.073, *majority update versus neutral*: $F_{(1,33)}$ = 5.4, p = 0.027, *majority ignore versus neutral*: $F_{(1,33)}$ = 1.2, p = 0.281, *majority ignore versus majority update*: $F_{(1,33)}$ = 1.6, p = 0.210; Figure 3.3C). This three-way interaction between incentive, trial-type and context was driven by incentive inducing greater slowing on update relative to ignore trials in the majority update context, but not in the other contexts (**BRMS**: 95% CI *majority update* = [-0.02, -0.00], *majority ignore* = [-0.01, 0.00], *neutral* = [-0.01, 0.02]; **rmANOVA**: *majority update*: $F_{(1,33)}$ = 4.6, p = 0.040, *majority ignore*: $F_{(1,33)}$ = 1.1, p = 0.305, *neutral*: $F_{(1,33)}$ = 0.5, p = 0.478). In the majority update context, incentive slowed responding on update trials, but had no effect on ignore trials (**BRMS**: 95% CI *update trials* = [0.00, 0.03], *ignore trials* = [-0.03, 0.01]; **rmANOVA**: *update trials*: $F_{(1,33)}$ = 3.9, p = 0.058, *ignore trials*: $F_{(1,33)}$ = 1.2, p = 0.282).

Incentive did not interact with the main effect of context in terms of either deviance (**BRMS**: 95% CI *majority ignore versus neutral* = [-0.12, 0.12], *majority update versus neutral* = [-0.14, 0.07], *majority ignore versus majority update* = [-0.08, 0.15]; **rmANOVA**: $F_{(2,66)}$ = 1.4, p = 0.252), trials correct (**BRMS**: 95% CI *majority ignore versus neutral* = [-0.04, 0.04], *majority update versus neutral* = [-0.03, 0.05], *majority ignore versus majority update* = [-0.05, 0.03]; **rmANOVA**: $F_{(2,66)}$ = 0.8, p = 0.466) or RT (**BRMS**: 95% CI *majority ignore versus neutral* = [-0.01, 0.01], *majority update versus neutral* = [-0.01, 0.01], *majority ignore versus majority update* = [-0.00, 0.01]; **rmANOVA**: $F_{(2,66)}$ = 0.3, p = 0.738).

Moreover, there was no main effect of incentive on either deviance (**BRMS**: 95% CI = [-0.05, 0.02]; **rmANOVA**: $F_{(1,33)}$ = 0.1e-7, p = 0.992), trials correct (**BRMS**: 95% CI = [-0.08, 0.11]; **rmANOVA**: $F_{(1,33)}$ = 0.1, p = 0.738) or RT (**BRMS**: 95% CI = [-0.00, 0.01]; **rmANOVA**: $F_{(1,33)}$ = 1.3, p = 0.255).

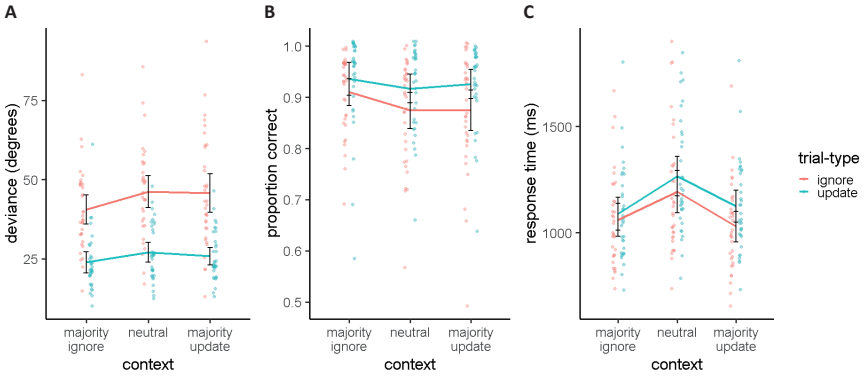

FIGURE 3.2 | **A** – Mean deviance, **B** – proportion of trials on which participants were correct and received a reward and C – mean response time as a function of context, separately for both trial-types. Dots represent mean scores per individual. Error bars represent 95% confidence interval.

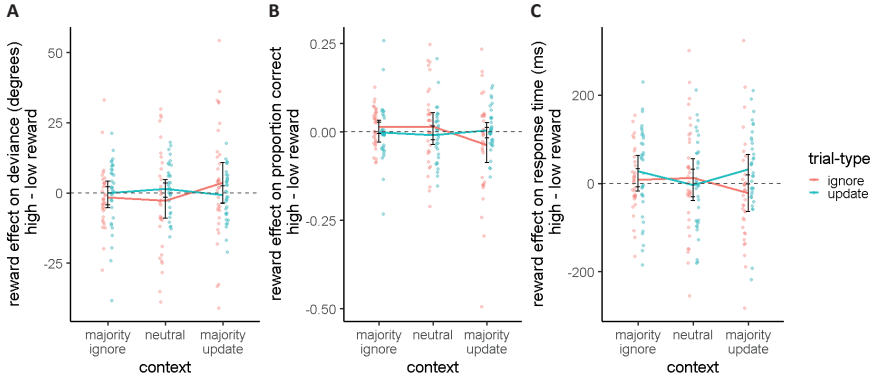

FIGURE 3.3 | Incentive effect (median split: high minus low incentive) on **A** – mean deviance, **B** – proportion of trials on which participants were correct and received a reward and **C** – mean response time as a function of context and trial-type. Dots represent mean scores per individual. Error bars represent 95% confidence interval.

Does the lack of meta-control effects reflect a failure-to-engage?

Although we did not find support for control strategy prioritization, we next considered a previous account arguing that people sometimes fail to engage in control, even though they are in principle able to do so (De Jong, 2000). In a task-switching paradigm,

participants' switch costs, were diminished when they had time to proactively prepare for a task-switch (De Jong, 2000; Nieuwenhuis & Monsel, 2002). However, switch costs were not eliminated, which was attributed to failures to engage in advance cognitive preparation on a portion of the trials. This failure-to-engage manifested itself most notably in the longer RTs, with individuals exhibiting disproportionately long RTs when they did not prepare for an upcoming trial.

It might be possible that here too, meta-level strategy prioritization is most prominently present for trials with the longer RTs and/or the larger deviances. To examine changes in longer RTs, associated with distributional skew, we used ex-Gaussian analyses for both deviance and RT. Ex-Gaussian models have three parameters: μ and η, reflecting the mean and standard deviation of the Gaussian part of the distribution and η, reflecting the mean and standard deviation of the exponential part, or the tail of the distribution consisting of the longest RTs or the largest deviance scores. We were interested in whether patterns of meta-level strategy prioritization would emerge when assessing η and whether this would be affected by the prospect of reward.

There was a non-significant trend for the interaction between context and trial-type on the τ parameter for deviance ($F_{(2,66)}$ = 2.7, p = 0.073). However, in contrast with our hypothesis that the τ parameter should be smaller for the high-frequent trial-type, participants' τ was smaller for update trials in the majority ignore context. Thus, the proportion of large deviance scores was relatively lower for update trials in the majority ignore context. Consistent with the analyses of mean deviance, the main effect of context on the τ parameter for deviance was significant ($F_{(2,66)}$ = 3.4, p = 0.039), with τ being smaller in the majority ignore context compared with both the majority update context ($F_{(1,33)}$ = 4.3, p = 0.046) and the neutral context ($F_{(1,33)}$ = 6.4, p = 0.017). There was no difference between the majority update and the neutral context ($F_{(1,33)}$ = 0.07, p = 0.792). There were no main or interaction effects of incentive on τ (all p > 0.109).

For RT we observed a numerical trend for an interaction between context and trial-type on τ ($F_{(2,66)}$ = 2.7, p = 0.078), which was similar as for the analyses of mean RT: participants' τ was larger for update trials in the majority update context, indicating a larger proportion of long RTs for update trials in the majority update context. Consistent with the analysis of mean RT above, distributional analyses of RTs revealed a main effect of context on τ ($F_{(2,66)}$ = 14.0, p = $4.0e^{-5}$). Compared with the neutral context, τ was lower for the majority ignore ($F_{(1,33)}$ = 28.0, p = $7.7e^{-6}$) and the majority update context ($F_{(1,33)}$ = 10.7, p = 0.003), potentially owing to practice effects. There were no differences between the majority ignore and the majority update context ($F_{(1,33)}$ = 1.9, p = 0.177). There were no main or interaction effects of incentive on τ (all p > 0.200).

Thus, ex-Gaussian analyses revealed no evidence for the predicted effects of meta-level strategy prioritization in terms of accuracy. However, consistent with our primary analyses of mean deviance, we observed a main effect of context on the distributional skew of deviance scores, such that the proportion of large deviance scores was lower in the majority ignore context.

Better performance on ignore trials following ignore trials than following update trials

The observation that participants performed better in the majority ignore context might represent a different, unpredicted form of meta-control. This performance improvement might have reflected the greater proportion of ignore trials, which prompted increases in meta-control on trials immediately following those more stable and demanding ignore trials. Therefore, we explored whether participants performed better on trials following ignore trials and whether this effect depended on the current trial-type and incentive motivation. Additionally, we explored whether participants were slower on update trials immediately preceded by update versus ignore trials, given our observation that participants were relatively slower on update trials in the majority update context than in the majority ignore context. To this end, we analyzed deviance, trials correct and RT as a function of trial-type, previous trial-type and incentive.

This revealed a main effect of previous-trial type on both deviance and trials correct, such that participants performed better following an ignore than an update trial (Deviance: **BRMS**: 95% CI = [-0.07, -0.01]; **rmANOVA**: $F_{(1,33)} = 14.8$, $p = 5.2e^{-4}$; Trials correct: **BRMS**: 95% CI = [0.00, 0.18]; **rmANOVA**: $F_{(1,33)} = 4.2$, $p = 0.049$). However, there was a significant interaction between trial-type and previous trial-type (Deviance: **BRMS**: 95% CI = [-0.08, -0.02]; **rmANOVA**: $F_{(1,33)} = 21.6$, $p = 5.2e^{-5}$; Trials correct: **BRMS**: 95% CI = [0.03, 0.20]; **rmANOVA**: $F_{(1,33)} = 17.9$, $p = 1.7e^{-4}$; Figure 3.4A-B). Performance on ignore trials was better following an ignore trial than following an update trial (Deviance: **BRMS**: 95% CI = [-0.14, -0.05]; **rmANOVA**: $F_{(1,33)} = 22.8$, $p = 3.6e^{-5}$; Trials correct: **BRMS**: 95% CI = [0.09, 0.31]; **rmANOVA**: $F_{(1,33)} = 16.6$, $p = 2.7e^{-4}$). However, previous trial-type did not affect update trials (Deviance: **BRMS**: 95% CI = [-0.04, 0.04]; **rmANOVA**: $F_{(1,33)} = 1.0$, $p = 0.328$; Trials correct: **BRMS**: 95% CI = [-0.16, 0.12]; **rmANOVA**: $F_{(1,33)} = 0.5$, $p = 0.488$). Thus, the greater proportion of trials following ignore trials in the majority ignore context might explain the performance improvement for ignore trials, but not for update trials. This trial-wise meta-control effect, i.e. the interaction between current trial-type and previous trial-type, was not affected by incentive (Deviance: **BRMS**: 95% CI = [-0.02, -0.04]; **rmANOVA**: $F_{(1,33)} = 9.2e^{-3}$, $p = 0.924$; Trials correct: **BRMS**: 95% CI = [-0.10, 0.07]; **rmANOVA**: $F_{(1,33)} = 0.2$, $p = 0.670$; Figure 3.5A-B), nor was there an

interaction between incentive and previous-trial type (Deviance: **BRMS**: 95% CI = [-0.03, -0.03]; **rmANOVA**: $F_{(1,33)}$ = 1.4, p = 0.250; Trials correct: **BRMS**: 95% CI = [-0.10, 0.06]; **rmANOVA**: $F_{(1,33)}$ = 0.5, p = 0.503).

There was no effect of previous trial-type on RT (**BRMS**: 95% CI = [-0.01, 0.00]; **rmANOVA**: $F_{(1,33)}$ = 2.7, p = 0.108), nor was there an interaction between previous trial-type and current trial-type (**BRMS**: 95% CI = [-0.00, 0.01]; **rmANOVA**: $F_{(1,33)}$ = 0.5, p = 0.495; Figure 3.4C). Incentive did not interact with previous trial-type (**BRMS**: 95% CI = [-0.00, 0.01]; **rmANOVA**: $F_{(1,33)}$ = 0.8, p = 0.378) or with the interaction between previous trial-type and current trial-type (**BRMS**: 95% CI = [-0.01, 0.00]; **rmANOVA**: $F_{(1,33)}$ = 0.05, p = 0.827; Figure 3.5C).

Following the observation of these sequential effects on accuracy, we examined whether the improvement on ignore trials following ignore trials differed across contexts. To that end, we analyzed deviance and trials correct as a function of trial-type, previous trial-type and context, leaving out incentive as a predictor due to the low number of trials. However, there was no effect of context on the interaction between trial-type and previous trial-type on deviance (**BRMS**: 95% CI *majority ignore versus neutral* = [-0.04, 0.04], *majority update versus neutral* = [-0.03, 0.06], *majority ignore versus majority update* = [-0.06, 0.03]; **rmANOVA**: $F_{(2,66)}$ = 0.5, p = 0.595) or trials correct (**BRMS**: 95% CI *majority ignore versus neutral* = [-0.15, 0.11], *majority update versus neutral* = [-0.14, 0.08], *majority ignore versus majority update* = [-0.11, 0.14]; **rmANOVA**: $F_{(2,66)}$ = 0.8, p = 0.470).

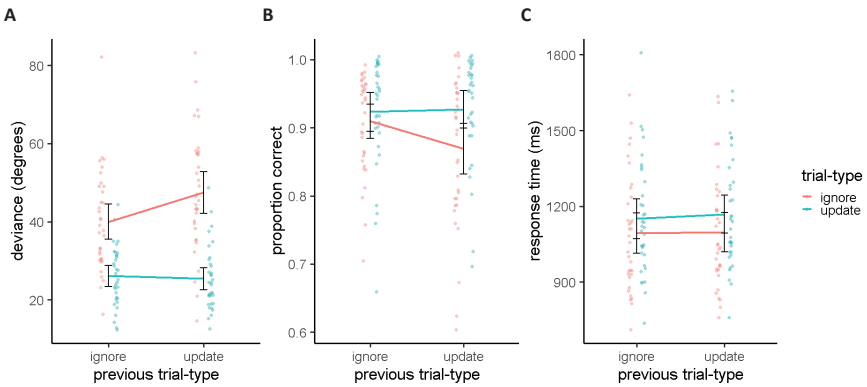

Figure 3.4. **A** – Mean deviance, **B** – proportion of trials on which participants were correct and received a reward and **C** – mean response time as a function of trial-type and the trial-type immediately preceding the current trial (previous trial-type). Dots represent mean scores per individual. Error bars represent 95% confidence interval.

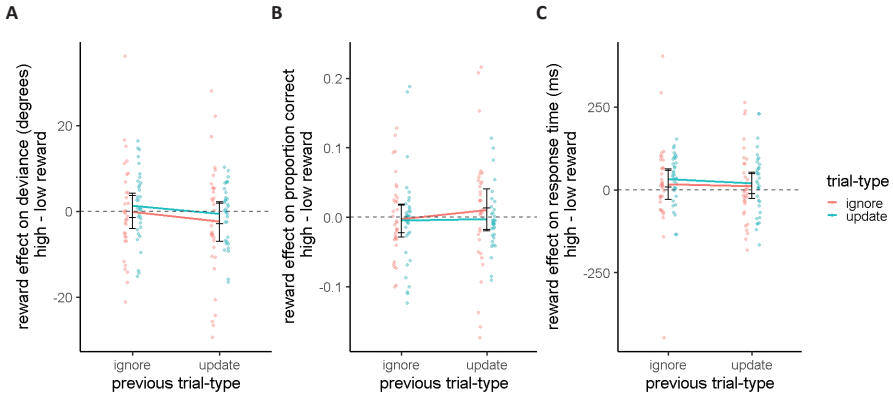

Figure 3.5. Incentive effect (median split: high minus low incentive) on **A** – Mean deviance, **B** – proportion of trials on which participants were correct and received a reward and **C** – mean response time as a function of trial-type and the trial-type immediately preceding the current trial (previous trial-type). Dots represent mean scores per individual. Error bars represent 95% confidence interval.

Discussion

Here we assessed whether incentive motivation promotes cognitive meta-control. We predicted that incentive motivation would favor the high-frequent task over the low-frequent task by increasing meta-level strategy prioritization (Braver, 2012; Braver et al., 2014). In contrast to our prediction, there was no interaction between trial-type and context on deviance or proportion correct. We expected participants to perform better on update trials in a context where the majority of the trials consisted of update trials and to perform better on ignore trials in a context where the majority of the trials consisted of ignore trials, and thus show a form of meta-control for the high-frequent task. However, we found no indication of this form of meta-level strategy prioritization in terms of accuracy. A subsequent exploratory ex-Gaussian analysis to specifically recover effects on trials with the largest deviance scores also revealed no effects of meta-level strategy prioritization on deviance. The absence of the predicted effect of meta-level strategy prioritization on accuracy prevents us from assessing our hypothesis that incentive increases strategy prioritization. Indeed, we did not find support for the hypothesized interaction between trial-type, context and incentive motivation.

A significant trial-type by context effect on response times indicated that participants were particularly slower on update trials in the majority update context relative to the majority ignore context, and this effect was potentiated when participants anticipated

being rewarded with more points. The interpretation of response times is unclear in this paradigm. Participants were instructed that they would receive the reward if their deviance were below a certain threshold, as long as they responded within the very liberal response window of 4 seconds. Therefore, they might well have responded more slowly to increase their accuracy, such that longer RTs would reflect enhanced caution. However, these slower RTs were not accompanied by improved accuracy and participants were instructed that they could potentially receive more reward if they completed more trials, implying that slower RTs would reflect poorer performance. Future analyses using drift diffusion (Ratcliff, 1978; Smith, 2016) or LATER (Pearson et al., 2014) models could offer a solution to this open question. According to these models, participants accumulate evidence until a certain decision threshold is reached. Although the number of trials in the current paradigm is too low, future studies with higher number of trials could assess whether the slower RTs reflect an increased threshold (i.e. enhanced caution) or a reduced rate of evidence accumulation (i.e. poorer memory representation).

The lack of predicted effects raises the question why participants did not engage in meta-level strategy prioritization, at least to enhance accuracy, particularly because they were explicitly instructed about the context manipulation at multiple timepoints? The lack of meta-level strategy prioritization is unlikely to reflect ceiling effects or a failure to process the task cues, because accuracy was increased in the majority ignore context compared with the other contexts.

One possibility is that the benefit associated with meta-level strategy prioritization did not weigh up against the effort cost (De Jong, 2000; Shenhav et al., 2013, 2017). According to the expected value of control (EVC) model, people decide whether to exert cognitive control based on the expected net value of control, which combines the expected payoff of exerting cognitive control and the expected subjective cost associated with exerting the amount of cognitive control necessary to achieve that payoff (Shenhav et al., 2013, 2017). The high percentage of trials rewarded (around 90%, see Figure 3.2B) might imply that it was not worth spending the selective effort cost to prepare for the high-frequent task at the expense of the low-frequent task. Participants could decide to only memorize the items from the phase they expected to be the relevant phase, that is the first phase in the majority ignore context and the second phase in the majority update context. However, they would then arguably only receive a reward on 67% of the trials, which is considerably lower than their default performance. The lenient threshold to obtain a reward was intentionally implemented to optimize the design for average reward manipulations (out of the scope of the current chapter), in order to preserve the random Gaussian distribution of received reward (see Methods). However, future studies could either implement a more stringent

threshold or adapt the incentive structure such that the amount of received reward is inversely and linearly related to deviance (see e.g. (Honig et al., 2020)).

Another possibility is that despite the lack of evidence for meta-level strategy prioritization, we did observe an interesting performance improvement, independent of trial-type, in the majority ignore context. This might reflect a different form of meta-control, where the majority ignore context triggered a nonselective improvement in effort, motivation or attention to the experiment. For ignore trials, but not for update trials, the context effect might have resulted from increased meta-control on a trial-wise level. The observation that participants performed better on ignore trials following ignore trials compared to update trials is akin to the Gratton effect: an incongruency effect, i.e. poorer performance on incongruent relative to congruent trials, is decreased following incongruent compared to congruent trials (Gratton et al., 1992). However, the previous trial-type did not affect performance on update trials. Thus, in addition to the trial-wise effect, the high proportion of the more demanding and stability-requiring ignore trials in the majority ignore context might have had a general positive effect on working memory by increasing task engagement, cognitive maintenance, or attention to the experiment. Incentive motivation also did not affect this form of meta-control.

Although this is in contrast with studies that reported positive effects of incentive motivation on meta-control (Chiew & Braver, 2016; Etzel et al., 2016), two previous studies could also not demonstrate an interaction between meta-control and incentive motivation (Soutschek et al., 2014, 2015). The first study examined behavioral effects on a Stroop task, in which trials were either preceded by a reward cue or not. The possibility for meta-control was manipulated by varying the frequency of incongruent versus congruent trials in a block, with a high frequency of incongruent trials generating conflict expectation and thereby allowing for preparation for the harder, incongruent trials. Both the possibility for meta-control and reward incentives reduced the congruency effect (i.e. slower responding on incongruent trials), but a combination of the two did not yield additional improvements (Soutschek et al., 2014). A follow-up fMRI study used a Stroop-like paradigm in which participants had to decide whether a face was that of a woman or a man, while ignoring the overlaid word “woman” or “man” (Soutschek et al., 2015). Again, the frequency of incongruent trials varied to manipulate conflict expectancy. Although conflict expectancy reduced conflict-related activity in the dorsal anterior cingulate cortex only when incentive motivation was high but not when incentive motivation was low, implying that motivation enhances meta-control, this was not accompanied by parallel effects on performance. Moreover, it has been shown using a working-memory paradigm that incentive motivation amplified patterns of enhanced representation of relevant stimuli and suppressed representation of irrelevant stimuli in terms of BOLD signal, without having reliable

behavioral effects (Krawczyk et al., 2007). Thus, it is possible that interactions between incentive motivation and meta-control did not surface at the behavioral level did have neural effects.

Another possibility is that meta-control would be affected by the average reward rate, rather than by the incentive associated with the current trial. Indeed, previous research has shown that the average reward rate, but not the reward on offer, affected effort exertion in terms of response times and accuracy on tasks involving perceptual detection, task-switching and stimulus-response compatibility (Beierholm et al., 2013; Guitart-Masip et al., 2011; Otto & Daw, 2019). Further analyses of the current dataset could determine whether average reward rate also affects meta-control.

Altogether, we find no evidence for effects of incentive motivation on meta-control in terms of accuracy. The pattern of effects on reaction times might raise the hypothesis that incentive motivation has elicited a proactively controlled increase in decision threshold, but sequential sampling modeling of both accuracy and RT data is required to confirm that hypothesis. Nevertheless, we remain puzzled by the insensitivity of the current paradigm to selective changes in accuracy by context and incentive motivation.

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CHAPTER 4

No evidence for a high reward context biasing cognitive flexibility over stability

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Abstract

Cognitive control requires a dynamic balance between the extent to which we focus and maintain current task representations (cognitive stability) and the extent to which we flexibly switch between representations (cognitive flexibility). It has been argued that rewards, through their action on dopaminergic processes in the striatum, promote cognitive flexibility by facilitating the gating of new information into working memory. Here, we assessed whether a highly rewarding task-environment, in which participants earn a high amount of reward, was associated with improved cognitive flexibility at the expense of cognitive stability using a working memory task. We expected that highly rewarding environments would not only improve cognitive flexibility in terms of performance, but also reduce the subjective cost of cognitive effort for tasks requiring flexibility, such that participants are more willing to engage in cognitive flexibility versus stability, measured with a subsequent cognitive effort discounting procedure. However, we did not find evidence that the reward environment affects the balance between cognitive stability and flexibility. Moreover, the general lack of any effects of reward environment suggests that the current paradigm is not sensitive to reward manipulations.

Introduction

Cognitive control refers to a set of mechanisms required for adaptively pursuing a (long term) goal, involving preparation and maintenance of rules to bias action and attention in working memory (Egner, 2017; Fuster, 1989; Monsell, 2003). Cognitive control, comprising functions such as working memory, attention and inhibition, is often associated with distractor resistance and persistent focus. However, in our dynamic environment, where goals change over the course of time and context, we also need to be able to flexibly adjust to the circumstances and allow new input and demands to enter our working memory. It is therefore important to dynamically balance the extent to which we focus and maintain current task representations (cognitive stability) versus the extent to which we flexibly switch between representations (cognitive flexibility).

Rewards have often been found to enhance cognitive control (Jimura et al., 2010; Krawczyk et al., 2007; Pessoa & Engelmann, 2010), but conflicting results have also been found, with rewards decreasing cognitive performance (Aarts et al., 2010, 2011; Chib et al., 2012; Mobbs et al., 2009; Zedelius et al., 2011). These contrasting effects of rewards have previously been hypothesized to stem from increases in striatal dopamine release induced by anticipated reward (Robbins & Everitt, 2007; Salamone et al., 2016; Schultz, 1997) and the observation that dopamine can have opposing effects depending on the type of the task at hand (Cools et al., 2010; Mehta et al., 2001, 2004). For example, administration of the dopamine receptor antagonist sulpiride impaired set-shifting but improved distractor resistance (Mehta et al., 2004). This is in agreement with observations in patients with Parkinson's disease, a disorder associated with striatal dopamine depletion, who show deficits in flexible task-switching (Cools et al., 2001), but enhanced cognitive stability on working memory paradigms when off but not on their dopaminergic medication (Cools et al., 2010; Moustafa et al., 2008). It has been argued that these task-dependent effects reflect dopamine's differential action in the prefrontal cortex and striatum (Cools & D'Esposito, 2011). Prefrontal dopamine would promote cognitive stability by increasing signal-to-noise (Durstewitz & Seamans, 2008; Vijayraghavan et al., 2007), whereas striatal dopamine would promote cognitive flexibility by facilitating the gating of new information into working memory (Frank et al., 2001; Hazy et al., 2007). In agreement with this hypothesis is the observation that dopamine depletion following 6-OHDA injection in marmosets had remarkably different effects depending on the site of injection: dopamine depletion in the frontal cortex impaired distractor resistance but improved attentional shifting, whereas dopamine depletion in the caudate nucleus improved distractor resistance and did not improve attentional shifting (Crofts et al., 2001). Similar results were found in a later study in humans, with the dopamine receptor agonist bromocriptine increasing neural activity in the prefrontal cortex

during distractor-resistance, while increasing neural activity in the striatum during task-switching (Cools et al., 2007).

Leveraging these insights to the effects of reward on cognitive stability versus flexibility, previous reasoning puts forward the hypothesis that anticipated reward would increase flexible control at the expense of stable control (Aarts et al., 2011). Indeed, it has been demonstrated, and replicated, using an incentivized Stroop task that human participants carrying the 9-repeat allele of the DAT1 transporter gene, which is predominantly expressed in the striatum and associated with higher striatal dopamine levels, showed greater reward-related improvements in task-switching than 10-repeat homozygotes (Aarts et al., 2010; van Holstein et al., 2011). Moreover, high reward increased switch-related neural activity in the striatum to a larger extent in the 9-repeat group (Aarts et al., 2010). These results strengthen the hypothesis that motivation increases cognitive flexibility through striatal processes.

In line with these effects of incentive motivation, inducing performance independent-affect, for example by having participants listen to happy or pleasant music or watch affective pictures, has been demonstrated to decrease perseverance but to increase distractibility (Dreisbach & Goschke, 2004) and to decrease maintenance capacity on the AX Continuous Performance Task, but benefit performance on the same task when goals suddenly changed (Dreisbach, 2006). Other researchers have found that positive affect increased susceptibility to distracting information (Rowe et al., 2007) and reduced focus after a trial with conflicting information (van Steenbergen et al., 2010). Thus, both incentive motivation and positive affect have been shown to enhance cognitive flexibility at the expense of cognitive stability

Here, we build on these insights by assessing whether a highly rewarding task-environment is associated with improved cognitive flexibility but reduced cognitive stability. Because in chapter 3 we did not find any effects of incentive motivation on cognitive control, we here manipulate the value of performance-independent rewards, such that participants perform a task in a rich and a poor environment.

In addition to expecting that rich environments would be associated with improved performance on tasks requiring cognitive flexibility, we also anticipated that these rich environments would be associated with reduced subjective cost of cognitive flexibility, such that participants are more willing to engage in cognitive flexibility versus stability, measured with a subsequent cognitive effort discounting procedure. This hypothesis is based on the proposal that the cost of cognitive control is equal to the average rewards received over time (Boureau et al., 2015; Niv et al., 2007; Otto & Daw, 2019): If the reward per trial in a task is high, it is more costly to focus on a current trial. As

cognitive flexibility requires less focus than cognitive stability, we here asked whether manipulating the reward value of the environment would also bias people towards greater cognitive flexibility in terms of costs in the context of a working memory task.

Methods

Participants

Thirty-five healthy and right-handed participants were recruited via SONA, the research participation system of the Radboud University. Participants had no history of neurological or psychiatric illness. The procedure of this study was approved by the local ethics committee (CMO region Arnhem-Nijmegen, The Netherlands; protocol 2014/288 version 1.4). Before the start of the experiment, subjects gave written consent. On top of an hourly rate of €8 per hour, participants were paid a monetary amount based on the number of points they received during the experiment (mean (SD) = €3.01 (€0.61), range €1.47 – €4.53). One participant was excluded from data analysis due to an incomplete dataset, resulting in 34 participants (28 women; age: mean (SD) = 22.9 (3.3), range 18 – 34).

Behavioral paradigm

The experiment consisted of four parts: participants completed a color sensitivity task, a color wheel working memory task to assess performance on cognitive stability and cognitive flexibility, a cognitive effort discounting paradigm to assess subjective costs of cognitive stability and flexibility, and a repetition of the working memory task. All tasks were performed on a computer running on Windows 7 and a screen resolution of 1920x1080p. The background color for all tasks was grey (R:200 G: 200 B: 200). All tasks were programmed in MATLAB version 2018a, using Psychophysics Toolbox Version 3.0.12.

Color sensitivity task

Participants first completed a color sensitivity task measuring the ability to detect and distinguish the colors in the main experiment. This task consisted of 12 trials where they had to match the color of a square in the center of a color wheel to the corresponding color on the wheel, by moving the mouse toward the wheel. Once they reached a color on the wheel, that color was taken as their response. If the average deviation of the response from the true color was more than 15 degrees, the task was assessed again. Participants would be excluded after a second failure.

The color wheel was created with the HSV MATLAB color map and was divided into 12 parts, each from which one color was randomly chosen to be the target color. The orientation of the color wheel was randomized across trials. After each trial, a first black line confirmed the response and a second line indicated the true color. Additional feedback conveying the absolute number of degrees to which the response deviated from the true color (deviance) was given if the deviance was below 10 degrees: e.g. 'Good job! You deviated only 4 degrees!'. Participants were instructed to answer precisely, but not to take too much time to respond. There was no maximum response time, but participants were instructed to first determine their response and only then move their mouse as fast as possible toward the wheel.

Color wheel working memory task

The color wheel task is a delayed response working memory task where participants view an array of colors and, after a delay, report the color of one probed item from the array (Prinzmetal et al., 1997; Wilken & Ma, 2004). We employed a version of the task that distinguishes between distracter resistance and flexible updating (Papadopetraki et al., 2019). A visual representation is depicted in Figure 1A. On each trial, colored items were presented in the middle of the screen, with the letter 'M' for 'memorize' in the middle. During this encoding phase, participants had 500ms to remember the colors of the items, after which there was a delay of 500ms during which a fixation cross was shown. During a subsequent interference phase, a new set of colored items appeared on screen, with one of two letters in the center. 'I' for 'ignore': participants had to ignore the new items while still remembering the old set of items; 'U' or 'update': participants now had to memorize the new set of items and forget the old items. This new set of squares remained on screen for 500ms, followed by a second delay phase. Depending on the task type, distractor resistance (ignore) or flexible updating (update), this delay lasted either 500ms or 1500ms, respectively, so that the time interval between the relevant stimuli (encoding phase for ignore and interference phase for update) and the probe phase was matched between task types. During this probe phase, a color wheel appeared on screen together with one highlighted frame that indicated the location of the color that should be reported. Participants had 4000ms to indicate the color of this target location by moving the mouse towards the corresponding color on the color wheel. No feedback was given on accuracy. If participants did not respond within 4000ms, a message was presented for 500ms in the center of the screen: 'Please respond faster!' Participants were instructed to always keep their eyes fixed on the center of the screen during the entire task.

To manipulate the richness of the environment, participants were instructed that they would complete several blocks of the task: half of the blocks in a rich environment and the other half in a poor environment. The two environments were indicated with either

a checkered or a dotted background pattern, counterbalanced across participants, and one of two sounds at the start of the trial, as shown in Figure 1A. They received 50 points for each trial in the rich environment and 10 points for each trial in the poor environment. Importantly, in Chapter 3 we did not find any reliable effects of performance-contingent rewards and it has been observed earlier that contingent and non-contingent rewards have different effects on performance (Braem et al., 2013; Grogan et al., 2020; Manohar et al., 2017). Moreover, it has been observed that the average reward rate, but not by the instrumental immediate reward offered on a trial affected performance (Beierholm et al., 2013; Guitart-Masip et al., 2011; Otto & Daw, 2019). We therefore adjusted the reward scheme such that obtaining the points was not contingent on performance to more closely mimic a "Pavlovian" reward environment rather than a direct action-outcome association. The obtained points were accumulated and proportionally converted into a monetary bonus.

Before the start of the task, participants read the instructions and completed two practice rounds. The first practice round consisted of 32 trials served to familiarize the participants with the distinction between update and ignore, without the environment manipulation. The second practice round introduced the two environments and consisted of 4 blocks of 8 trials each. The two environments were counterbalanced over blocks in an ABBA order. The actual task consisted of 8 blocks of 8 trials each, with the two environments counterbalanced across blocks in an ABBABAAB order. The number of items (set size) was either 1 or 3. All combinations of set size (1 or 3) and task type (ignore or update) were repeated twice within each block. All color sets were equal across task types and environments but randomized between blocks to minimize the chance that participants remembered them. The colors that were presented during the encoding phase of ignore trials were the same as the colors that were presented during the interference phase of update trials and vice versa. The target colors were the same for both task types.

The total duration of the task, including instruction and practice trials, was approximately 50 minutes.

Cognitive effort discounting task

The subjective cost of cognitive control exertion in the color wheel working memory task was assessed using a choice task based on the cognitive effort discounting paradigm (COG-ED; (Westbrook et al., 2013)), administered after participants completed the color wheel task. Participants repeatedly had to choose between two different versions of repeating the color wheel working memory task for different amounts of money (Figure 1B). The amount of money offered was titrated over 6 iterations and

the difference in final amount between the versions was taken as the cost of cognitive effort (see below). To test the key effect of environmental richness on subjective costs, choices were completed in both a rich and a poor environment.

The version pairs were divided into two types: 1) choosing between redoing the color wheel task or not having to redo the task (task versus no redo) and 2) direct comparisons between redoing different ignore versus update or high versus low set size color wheel versions (direct comparison). The "task versus no-redo" choices always asked whether the participant would rather do a particular of the color wheel task again or whether they would rather not redo the task, which meant that they would be free to do what they wanted for an equal length of time while staying in the testing room (They could use the computer, their phone, etc.). The redo version was further specified by task type and set size (update 1; update 3; ignore 1; ignore 3), so that participants were instructed that 75% of trials during the redo would consist of trials of the chosen task type and set size. The remainder of the redo trials would be randomly divided among all task type and set size combinations. The "direct comparison" choices compared whether participants would rather redo set size 1 for less money versus set size 3 for more money (comparing set size: update 1 versus update 3; ignore 1 versus ignore 3) or whether participants would rather redo update versus ignore trials (comparing task type: update 1 versus ignore 1; update 3 versus ignore 3). This resulted in 8 unique version pairs.

Participants were initially offered €2 for both versions. The offer for the version that was a priori assumed to be the easier one of the versions was then stepwise titrated over 6 iterations until the participant did not prefer one version over the other anymore (Figure 1B). In the "task versus no redo" version, the offer for the no redo option was always adjusted and the offer for the task option was fixed at €2.00, whereas in the "direct comparison" version, the offer for the lower set size or the update option was adjusted and the offer for the higher set size or the ignore option was fixed at €2.00. For example, if on a given trial a "no redo" version of the task was chosen over an "update 1" version, the offer for "no redo" was decreased. If instead the "update 1" version was chosen, the offer for "no redo" was increased. Each adjustment was half as much as the prior adjustment, with a final adjustment of €0.03125 following their sixth choice. This titration procedure was conducted for each unique version pair. The final amount after the last adjustment was taken as the participant's indifference point. That is, the participant does not prefer one version for a lower amount of money over another version for a higher amount of money. For example, if the final amount is €0.84 for "no redo" versus €2.00 for "update 1", the participant is willing to forego €1.16 in exchange for not having to redo the task instead of having to redo a "mostly update 1" version of the task. Thus, the cost of effort for the "update 1" version is €1.16.

The location of the versions was randomized (top/bottom; left/right). Participants selected their preferred version by pressing the '1' key for the version on the left and the '2' key for the version on the right, using their right hand. To prevent participants from feeling rushed in their decision-making, but to discourage them from taking a long break, the maximum response time was set to 22 seconds, after which a warning message appeared ('Too slow!'), and the same trial was repeated. To encourage participants to make a deliberate choice, a warning message appeared on the screen if participants responded within 500ms ('Please consider both options carefully!') and the same trial was repeated.

After a short practice block in which each version pair was presented once (resulting in 8 trials), participants completed four blocks of 48 choices each (6 iterations for each of the 8 version pairs). To test the key effect of environmental richness on subjective costs, each block was completed in either a rich or a poor environment, indicated by the same background pattern and tone associated with the respective environment in the color wheel task. The environments were counterbalanced in an ABBA order. Each version pair was thus run through the titration procedure twice under each environment. The average cost of effort across the two runs was taken as the final subjective cost.

Participants were informed that one of their choices would be randomly selected for them to complete. Moreover, they were instructed that the richness of the environment in which they made the selected choice determined the richness of the environment in which they repeated the color wheel working memory task, and thus the number of points they would obtain per trial. For example, if their selected choice was to redo the update 1 version for €1.50 (versus "No redo" for €2.00) and the environment in which that choice was made was rich, this meant they would receive €1.50 associated with their choice, that most of the trials would be update trials with set size 1, and that they would additionally receive 50 points for each trial, which would later be converted into a monetary amount. Alternatively, if their selected choice was to not redo the task for €0.50 and the environment in which that choice was made was rich, they received €0.50 associated with their choice and they would still receive the 50 points per trial they would have received by repeating the task. This was to purely test the effect of the environment on participants' choices and to not bias them to choose the redo version based on the extra money they would receive for completing trials in a rich environment.

The total duration of the task, including instruction and practice trials, was approximately 25 minutes.

Subjective cost questions on the color wheel working memory task

In addition to quantifying the subjective cost using the subsequent discounting procedure, we also explored the subjective cost during the performance of the color wheel task. After each block of trials, participants had to indicate on a visual analogue scale how much money they would give up to not have to repeat a certain task condition again (4 questions, one for each combination of set size and task type), ranging from €1 to €2.

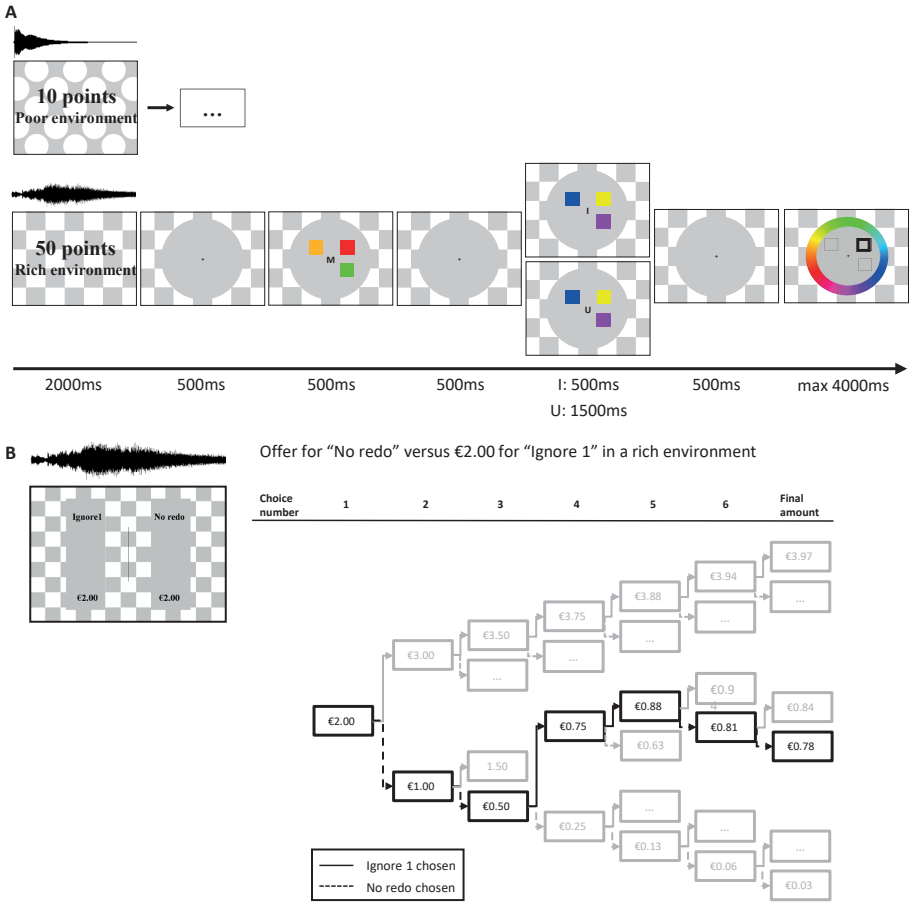

FIGURE 4.1 | Behavioral tasks. **A** – Schematic of the color wheel working memory task. Participants receive 10 points for each trial completed in a poor environment (top) and 50 points for each trial completed in a rich environment (bottom). A low tone is played at the start of a poor environment and a high tone is played at the start of a rich environment. The two background patterns associated with the richness of the environment are counterbalanced across participants. M = 'memorize': participants have to remember the colors; I = 'ignore': participants have to ignore the new colors while still remembering the previous colors. U = 'update': participants have to remember the new colors and forget the previous colors. **B** – Schematic of the cognitive effort

discounting task. Participants repeatedly choose between two versions of the color wheel task for various amounts of money. The offer for one of the versions is titrated until arriving at a final amount, which is taken as the offer for that version at which the participant does not prefer one version over the other.

Data analysis

Performance measures on the color wheel task included the absolute number of degrees with which the response deviated from the correct color (deviance) and the response time (RT) for each participant. Subjective cost of the color wheel task was calculated as the mean difference between the final amount and the initial €2 (discounting task; primary measure of subjective cost) or as the amount of money a participant was willing to give up to avoid having to repeat a certain task condition again (questions during the color wheel task; exploratory measure). All trials on the color wheel task with a response time below 200 ms were excluded. Outliers were a priori defined as those participants whose median deviance, median RT, or average subjective cost deviated more than three standard deviations from the average across participants. This did not result in any exclusions.

We analyzed our data in R version 3.6.0 (R Core Team, 2018) using a combination of primary Bayesian mixed effects modeling supplemented by repeated-measures ANOVAs (rmANOVAs) on summary data to confirm the results and to accommodate readers who are used to interpreting frequentist statistics.

The Bayesian mixed effects models were performed using the brm function from the brms package (Bürkner, 2017). Deviance, RT and subjective cost on the color wheel task were analyzed on a trial-by-trial level, whereas subjective cost as measured by the discounting task was taken as the average cost across runs. The family functions used were lognormal for deviance and RT and gaussian for subjective cost. The model included the main effects of the predictors set size (1 or 3), task type (ignore, update) and environment (poor, rich) and their interactions as fixed effects, and random intercepts and slopes per participant for the same effects. The categorical variables were coded as sum-to-zero contrasts. We used default brms-priors. The model was fit using four chains with 10,000 iterations each (5,000 warm-up) and were inspected for convergence. Coefficients were considered statistically significant if the 95% posterior credible intervals did not overlap with zero. The rmANOVAs were performed on median deviance, median RT and mean subjective cost and included the within-subjects factors set size, task type and environment. The analyses were performed using the ezANOVA function from the ez package (Lawrence, 2016). Data are visualized using raincloud plots (Allen et al., 2018).

Results

No effect of reward environment on performance on the color wheel working memory task

Consistent with earlier studies using a similar paradigm (Hofmans et al., 2020; Papadopetraki et al., 2019), deviance was higher (**BRMS**: 95% CI = [-0.66, -0.48]; **rmANOVA**: $F_{(1,33)}$ = 66.0, p < 0.001) and responses were slower (**BRMS**: 95% CI = [-0.14, -0.10]; **rmANOVA**: $F_{(1,33)}$ = 113.0, p < 0.001) on trials with a higher set size. The effect of task-type on deviance depended on set size (**BRMS**: 95% CI = [-0.23, -0.11]; **rmANOVA**: $F_{(1,33)}$ = 39.5, p < 0.001; Figure 2A), such that deviance was lower on update compared with ignore trials for set size 3 (**BRMS**: 95% CI = [0.28, 0.47]; **rmANOVA**: $F_{(1,33)}$ = 41.5, p < 0.001), but there was no significant difference for set size 1 (**BRMS**: 95% CI = [-0.05, 0.11]; **rmANOVA**: $F_{(1,33)}$ = 0.9, 7 = 0.352). Participants were slower on update than on ignore trials (**BRMS**: 95% CI = [-0.04, -0.01]; **rmANOVA**: $F_{(1,33)}$ = 8.6, p = 0.006). The interaction effect between task type and set size on RT was not significant (**BRMS**: 95% CI = [-0.01, 0.01]; **rmANOVA**: $F_{(1,33)}$ = 0.3, p = 0.605; Figure 2B).

Contrary to our predictions, there was no effect of reward environment on performance on update versus ignore trials either in terms of deviance (*environment x task type*: **BRMS**: 95% CI = [-0.04, 0.08]; **rmANOVA**: $F_{(1,33)}$ = 1.2, p = 0.283; Figure 2C) or RT (*environment x task type*: **BRMS**: 95% CI = [-0.02, 0.01]; **rmANOVA**: $F_{(1,33)}$ = 1.3, p = 0.267; Figure 2D). There was also no interaction between environment, task type and set size (*Deviance*: **BRMS**: 95% CI = [-0.06, 0.06]; **rmANOVA**: $F_{(1,33)}$ = 2.4, p = 0.129; *RT*: **BRMS**: 95% CI = [-0.01, 0.01]; **rmANOVA**: $F_{(1,33)}$ = 0.3, p = 0.610), no interaction between environment and set size (*Deviance*: **BRMS**: 95% CI = [-0.07, 0.05]; **rmANOVA**: $F_{(1,33)}$ = 2.1, p = 0.155; *RT*: **BRMS**: 95% CI = [-0.01, 0.01]; **rmANOVA**: $F_{(1,33)}$ = 0.4, p = 0.544) and no main effect of environment (*Deviance*: **BRMS**: 95% CI = [-0.08, 0.04]; **rmANOVA**: $F_{(1,33)}$ = 1.7, p = 0.205; *RT*: **BRMS**: 95% CI = [-0.01, 0.02]; **rmANOVA**: $F_{(1,33)}$ < 0.1, p = 0.943).

No effect of reward environment on the subjective cost of working memory effort

Cognitive effort versus rest

Next, we assessed whether reward environment affected the subjective cost of cognitive effort differentially for ignore and update trials. To that end, we first computed the subjective cost of effort relative to rest, or the No redo option. This revealed a significant effect of set size, such that the subjective cost was higher for set size 3 compared with set size 1 (**BRMS**: 95% CI = [-0.33, -0.17]; **rmANOVA**: $F_{(1,33)}$ = 46.7,

p < 0.001). The effect of task type was not significant (**BRMS**: 95% CI = [-0.02, 0.09]; **rmANOVA**: $F_{(1,33)}$ = 1.6, p = 0.208), nor was the interaction between task type and set size (**BRMS**: 95% CI = [-0.06, 0.04]; **rmANOVA**: $F_{(1,33)}$ = 0.1, p = 0.730; Figure 3A).

Contrary to our hypothesis, we did not find a significant interaction between reward environment and task type (**BRMS**: 95% CI = [-0.03, 0.03]; **rmANOVA**: $F_{(1,33)}$ < 0.1, p = 0.993; Figure 3B). There was also no interaction between reward environment, task type and set size (**BRMS**: 95% CI = [-0.00, 0.05]; **rmANOVA**: $F_{(1,33)}$ = 3.2, p = 0.085), no interaction between reward environment and set size (**BRMS**: 95% CI = [-0.04, 0.02]; **rmANOVA**: $F_{(1,33)}$ = 0.6, p = 0.431) and no main effect of reward environment (**BRMS**: 95% CI = [-0.01, 0.07]; **rmANOVA**: $F_{(1,33)}$ = 2.4, p = 0.131).

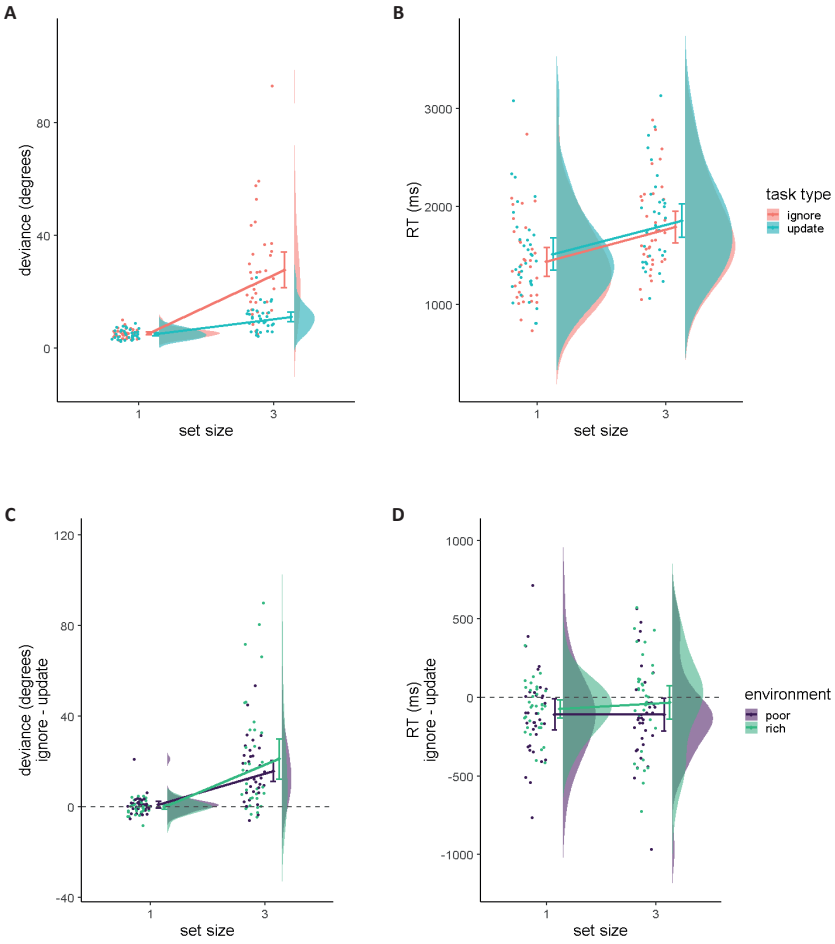

FIGURE 4.2 | Performance on the color wheel working memory task. Median deviance (A) and median reaction time (B) as a function of set size and task type. Difference between ignore and update trials in terms of median deviance (C) and median reaction time (D) as a function of set size and reward environment. Individual jittered datapoints and data distribution are shown. Error bars represent 95% confidence interval. N = 34.

Update versus ignore

We then assessed the choice trials with a direct comparison between ignore and update trials. The offer for the ignore option was fixed at €2.00, with a calibrated offer for the update option. Therefore, a subjective cost above 0 indicated that participants preferred update over ignore, whereas a subjective cost below 0 indicated that participants preferred ignore over update. An initial t-test across both set sizes and both reward environments revealed no difference in cost between ignore and update trials (mean = -0.004, t = -0.07, p = 0.944). This subjective cost did not depend on reward environment (**BRMS**: 95% CI = [-0.05, 0.04]; **rmANOVA**: $F_{(1,33)}$ = 0.1, p = 0.743), set size (**BRMS**: 95% CI = [-0.09, 0.16]; **rmANOVA**: $F_{(1,33)}$ = 0.3, p = 0.609), or the interaction between set size and reward environment (**BRMS**: 95% CI = [-0.03, 0.06]; **rmANOVA**: $F_{(1,33)}$ = 0.4, p = 0.554; Figure 3C).

Low versus high set size

Lastly, we assessed the choice trials with a direct comparison between set size 1 and 3. The offer for the set size 3 option was fixed at €2.00, with a calibrated offer for the set size 1 option. Therefore, a subjective cost above 0 indicated that participants preferred set size 1 over set size 3, whereas a subjective cost below 0 indicated that participants preferred set size 3 over set size 1. An initial t-test across both task types and both reward environments revealed a significant higher cost of set size 3 compared with set size 1 (mean = 0.72, t = 13.2, p < 0.001). However, this subjective cost did not depend on reward environment (**BRMS**: 95% CI = [-0.02, 0.04]; **rmANOVA**: $F_{(1,33)}$ = 0.5, p = 0.476), task type (**BRMS**: 95% CI = [-0.11, 0.13]; **rmANOVA**: $F_{(1,33)}$ < 0.1, p = 0.843), or the interaction between task type and reward environment (**BRMS**: 95% CI = [-0.04, 0.04]; **rmANOVA**: $F_{(1,33)}$ < 0.1, p = 0.968; Figure 3D).

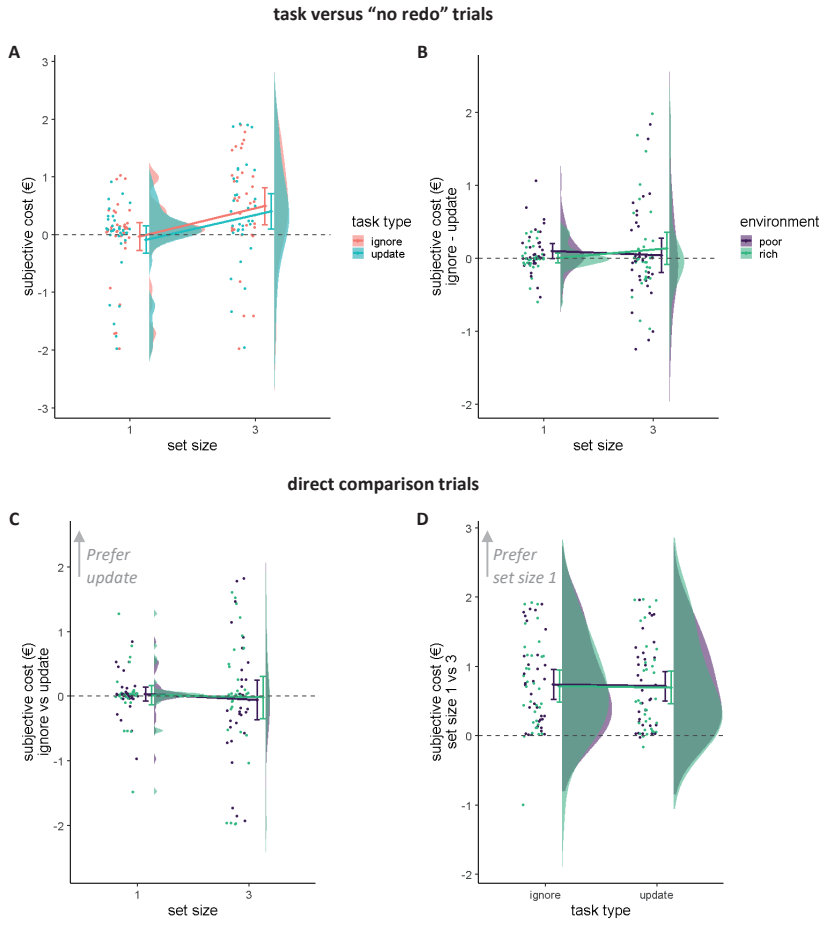

FIGURE 4.3 | Subjective cost of performing the color wheel working memory task. **A** – Subjective cost of performing the color wheel working memory task versus rest as a function of set size and task type, as measured by the task versus no redo trials of the discounting task. **B** – Difference in subjective cost between ignore and update trials as a function of set size and reward environment, as measured by the task versus no redo trials of the discounting task. **C** – Subjective cost of performing ignore versus update trials as a function of set size and reward environment, as measured by the direct comparison trials of the discounting task. D – Subjective cost of performing set size 3 versus set size 1 as a function of task type and reward environment, as measured by the direct comparison trials of the discounting task. Individual jittered datapoints and data distribution are shown. Error bars represent 95% confidence interval. *N* = 34.

Subjective cost questions

We explored the subjective cost measured during the color wheel working memory task. This revealed no effect of either reward environment, task type or set size (main effects and interactions; all 95% CI overlapping with 0; all $F(1,33) < 1.9$; all $p > 0.175$). We additionally evaluated whether subjective cost as measures using these questions

during the color wheel task correlated with subjective cost of the same trial type as measured using the discounting task. This was not the case, as revealed by Pearson's correlations for each trial type (all $r < 0.24$, all $p > 0.166$).

Participants were aware of the difference between the reward environments

The lack of effects of reward environment poses the question whether the participants were aware of the manipulation of reward environment. After the task instructions but before the start of the task, participants were asked by the experimenter to explain the task in their own words to verify that they had understood the task. Furthermore, after finishing the experiment, participants were asked whether they had noticed the different manipulations cueing the reward environment ("Did you notice the difference in tone between the rich and poor environments while playing the game?" and "Did you notice the difference in background patterns between the rich and poor environments while playing the game?"; answer options: yes, no). The majority of participants indeed reported that they were aware of these manipulations: 87% of the participants was aware of the difference in tone; 71% of the participants was aware of the difference in background pattern.

Discussion

According to the hypothesis that rewards enhance cognitive flexibility at the expense of cognitive stability (Aarts et al., 2011; Cools & D'Esposito, 2011; Dreisbach, 2006; Dreisbach & Goschke, 2004; Rowe et al., 2007; van Steenbergen et al., 2010), the present study assessed whether performing a task in a rich environment improved cognitive flexibility at the expense of cognitive stability, in terms of both working memory performance and subjective cost of cognitive effort. This hypothesis was further inspired by the average reward rate literature, which argues that it is more costly to focus on a current task when the average reward received over previous tasks is high (Boureau et al., 2015; Niv et al., 2007; Otto & Daw, 2019). We asked whether this high cost of focus would also manifest itself in the context of a working memory task, such that a high reward value of the environment would generate relatively lower costs for flexibility versus stability. However, in contrast to our hypothesis, we did not observe any effects of reward environment on the balance between stability and flexibility in cognitive performance or subjective cost of effort.

The average reward rate proposal was inspired by literature on patch-leaving and foraging, it has been shown that when the reward value of alternative options is high, animals or people are biased to leave their current patch to explore alternative patches

rather than to continue to exploit the current patch (Charnov, 1976; Constantino & Daw, 2015; Kolling et al., 2012; Le Heron et al., 2020). As described by the Marginal Value Theorem, engaging with or exploitation of an option is only beneficial as long as the received rewards are higher than the rewards you would expect to receive by exploring other options. As the reward that can be received from a current option decreases over time, a foraging animal should leave the current patch as soon as the reward falls below the expected value of other options, in other words, below the opportunity cost of time (Charnov, 1976). Thus, high rewards for alternative options would bias a person towards flexibility at the expense of stability. An important caveat in our present design was that although a rich environment was meant to increase the subjective cost of effort by increasing the average reward rate over time (Boureau et al., 2015; Niv et al., 2007; Otto & Daw, 2019), this manipulation could have in fact gone the opposite way. Participants were instructed about the points they would receive in a low and high reward environment and about the blocked design. Because the environments were blocked, currently being in a high reward environment could be interpreted as the rewards per trial currently being higher than the rewards per trials on average, across all blocks. Thus, a high reward environment could have been experienced as a high reward for the current task amidst a relatively lower reward for alternative tasks or blocks, resulting in effects opposite of our hypothesis: a bias toward stability rather than flexibility. Still, we did not find any effects of reward environment, in neither direction.

It is worth noting that although our hypothesis involved the effect of reward environment on the balance in performance between trials requiring stability versus flexibility, one might also have expected a general invigorating effect of a high reward environment. Based on earlier research, a high average reward rate as experienced in a rich environment, would increase the speed of responding (Beierholm et al., 2013; Guitart-Masip et al., 2011; Niv et al., 2007; Otto & Daw, 2019): If the reward per trial is high, it is costly to focus on the current trial for too long and it is beneficial to rapidly finish the current trial to move on to the next one. However, we did not find any main effects of reward environment.

This lack of reward effects raises the question whether participants were aware of the reward environment. Initial verification by the experimenter before the start of each task and the later debriefing questions indicated that participants were indeed aware of the different environments during the task. However, it might have been the case that participants did not cognitively process this information during the trial, even though they were aware of the different environments. We deliberately opted for rewards that were performance-independent, because we had previously found no effects of performance-contingent rewards and it had been observed that contingent

and non-contingent rewards have different effects on performance (Braem et al., 2013; Manohar et al., 2017). However, in combination with the relative complexity and the fast pace of the color wheel task, this might have discouraged participants from using this information to adapt their cognitive control strategy, so they could use their cognitive resources to process information that was relevant for their performance. Future work might assess the effect of performance-contingent reward environments or paradigms similar to patch-leaving tasks on the balance between cognitive flexibility and stability.

In the "versus No redo" version of the discounting choice task, participants would always receive the number of points per trial associated with the environment in which the choice was made, even if the selected choice was the No redo option. It would have been more likely to find a main effect of reward environment if participants were to receive those points only if they selected the Redo option: Participants would probably be more inclined to choose the Redo (update or ignore) option in a rich environment than in a poor environment, so they could maximize their points. However, a strong inclination to choose the Redo option regardless of the trial-type would have diminished the chance to find any differential effects on stability versus flexibility, our main effect of interest.

We did not replicate the earlier finding by Papadopetraki and colleagues that, using the same color wheel paradigm, participants preferred update trials over ignore trials (Papadopetraki et al., 2019). This distinction in preference between the two task types was also not observed in another study, even though participants performed better on update than on ignore trials (Hofmans et al., 2020). A difference between these studies was that in the Papadopetraki study, participants had to make choices both between update and ignore trials and between task (update or ignore) and rest, while in the Hofmans study participants only chose between task (update or ignore) and rest, which might have restricted the distinction participants made between the two task types. However, in the current paradigm, we reintroduced the direct comparison between update and ignore, without observing any differences in subjective cost. A possible explanation for the difference in effects is that the pacing of the trials was faster in both the study by Hofmans and colleagues and the current study than in the study by Papadopetraki and colleagues. In the current paradigm, both the duration of the stimuli and the delays was 500ms instead of the 2000ms in the earlier study. It has recently been proposed that a decision is made between two strategy representations (here, update or ignore) based on a control signal that accumulates over time for both types of strategy until one of the two response thresholds is reached (Musslick et al., 2018). The intensity of this control signal reflects the experienced cognitive cost, as one would have to exert more effort into the accumulation of the control signal. Based

on the better performance on update relative to ignore trials, we might assume that an update representation is more automatic than an ignore representation. It could then be speculated that when there is not enough time to accumulate control, which might be the case in the fast-paced current paradigm, one would still perform well on update trials, but not on the more control-demanding ignore trials. Therefore, the intensity of the control signal, or the exerted effort is too low to result in a distinctive subjective cost of ignore relative to update. This is supported by the observation that the median deviance on ignore trials, but not update trials, with a set size of 3 is higher in the current study than in the study by Papadopetraki et al. (ignore: ~30 versus ~15; update: ~10 versus ~10), suggesting that participants exerted less control for ignore trials in the current study, possibly resulting in lower subjective costs for ignore trials.

In conclusion, our results do not provide evidence that the reward environment, where rewards are not performance-contingent, affects the balance between stability and flexibility in a working memory paradigm. Moreover, the general lack of any effects of reward environment, together with earlier results that show no effect of performance-contingent immediate reward (Chapter 3), might suggest that the current paradigm is not sensitive to reward manipulations.

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CHAPTER 5

Reward motivation and cognitive control: differential effects on stability and flexibility?

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Abstract

Cognitive control is known to be sensitive to changes in incentive motivation. However, contrasting effects of incentive motivation have been observed. Here we test a hypothesis derived from our understanding of striatal dopamine's role in cognitive control. Specifically, striatal dopamine is known to promote cognitive flexibility, but impair cognitive stability. Accordingly, we asked whether reward motivation enhances performance on tasks requiring cognitive flexibility at the expense of performance on tasks requiring cognitive stability. We applied a delayed match-to-sample task that distinguishes between trials requiring cognitive stability and cognitive flexibility, while also measuring trait impulsivity to capture potential individual variability in the effects of reward motivation. We found no effects of reward motivation on working memory accuracy. Instead, participants responded more slowly on high versus low reward trials. Exploratory analyses revealed that this slowing was selectively reduced on trials requiring flexibility, but not on trials requiring stability, and only in high-impulsive individuals, suggesting increased cognitive flexibility versus stability. Although preliminary and in need of replication, these initial results provide an interesting starting point for future behavioral studies using more sensitive paradigms, as well as for neuroimaging studies to determine the neural locus of effects of reward motivation.

Introduction

Appetitive motivation or anticipated rewards are generally thought to enhance cognitive control (Jimura et al., 2010; Krawczyk et al., 2007; Pessoa & Engelmann, 2010). However, reward incentives have also been demonstrated to decrease task performance depending on task demands (Aarts et al., 2010, 2011; Chib et al., 2012; Mobbs et al., 2009; Zedelius et al., 2011). These contrasting effects of rewards have previously been argued to reflect opposing effects of striatal dopamine depending on the type of the task at hand (Aarts et al., 2011; Cools et al., 2010; Salamone et al., 2016). For example, dopaminergic manipulations have been demonstrated to have, in the same individuals, opposing effects on tasks requiring cognitive stability, such as distractor-resistance, and tasks requiring cognitive flexibility, such as reversal learning and task-switching (Crofts, 2001; Mehta et al., 2001, 2004). Pharmacological manipulations as well as neurocomputational modeling suggest that striatal dopamine promotes flexible behavior and the updating of working memory representations by shifting the balance toward the direct 'go' pathway, away from the indirect 'no-go' pathway and thereby allowing new items to enter working memory (Collins & Frank, 2014; Cools, 2015; Cools & D'Esposito, 2011; Frank et al., 2001; Frank & O'Reilly, 2006; Hazy et al., 2007; Ueltzhöffer et al., 2015). This concurs with observations in patients with Parkinson's disease, characterized by striatal dopamine depletion, who exhibit cognitive inflexibility on task-switching paradigms (Cools et al., 2001), but enhanced cognitive stability on working memory paradigms when off but not on dopaminergic medication (Cools et al., 2010; Moustafa et al., 2008).

Here we leverage these insights about dopamine's contrasting effects on cognitive control to advance our understanding of reward effects on cognitive control. Specifically, in line with prior theorizing, we hypothesize that incentive motivation, by increasing striatal dopamine, enhances cognitive flexibility at the expense of cognitive stability (Aarts et al., 2011). This hypothesis generally concurs with the prior observations that positive affect decreases perseverance but increases distractibility on the AX Continuous Performance Task (Dreisbach & Goschke, 2004), while also benefiting performance on the same task when goals suddenly change (Dreisbach, 2006). We also consider the alternative hypothesis that incentive motivation, by increasing prefrontal dopamine, might increase the signal-to-noise of a memory representation, thereby improving cognitive stability versus flexibility (Durstewitz & Seamans, 2008), which is consistent with pharmacological studies showing that prefrontal dopamine activity is important for cognitive stability but impairs cognitive flexibility (Crofts et al., 2001; Fallon et al., 2017).

The effect of reward motivation was investigated using a delayed match-to-sample task that distinguishes between trials requiring cognitive stability and cognitive

flexibility (Papadopetraki et al., 2019). We predict that the promise of reward improves accuracy on trials requiring flexibility but impairs accuracy on trials requiring stability. Moreover, based on prior work demonstrating large individual variability in the effects of dopamine on cognitive control and working memory, we stratified our reward effects by trait impulsivity (Clatworthy et al., 2009; Cools et al., 2007), which itself implicates striatal dopamine (Buckholtz et al., 2010; Cools et al., 2008; Dalley et al., 2007; Kim et al., 2013; Landau et al., 2009; Lee et al., 2009). Given the presumed positive link between trait impulsivity and dopamine release (Buckholtz et al., 2010), we expected enhanced dopamine release in response to rewards and therefore stronger effects in more impulsive individuals.

METHODS

Participants

Forty healthy and right-handed participants (22 women; age range = 18-34) were recruited via SONA, the research participation system of the Radboud University. Participants had no history of neurological or psychiatric illness. The procedure of this study was approved by the local ethics committee (CMO region Arnhem-Nijmegen, The Netherlands; protocol 2014/288 version 1.4). Before the start of the experiment, subjects gave written consent. Participants were paid 8 euro per hour plus a bonus contingent on their performance, ranging from 2.68-5.37 euro. All participants were included for data analysis.

General procedure

The study consisted of two sessions, with at least a week in between (range 7-14 days). On the first day, participants completed a color sensitivity task (1 minute), a short color wheel working memory task to familiarize participants with the task (12 minutes), and a cognitive effort discounting paradigm not described in the current paper (22 minutes). On the second day, participants completed a rewarded version of the color wheel working memory task. All tasks were performed on a computer running on Windows 7 and a screen resolution of 1920x1080p. The background color for all tasks was grey (R:200 G: 200 B: 200). All tasks were programmed in MATLAB version 2016b, using Psychophysics Toolbox Version 3.0.12.

Color wheel working memory task

Color sensitivity task (day 1)

The color sensitivity task measured the ability to detect and distinguish the colors in the main experiment. Participants completed 12 trials where they had to match the color of a square in the center of a color wheel to the corresponding color on the wheel, by clicking on the color wheel. Performance on the color sensitivity task was successful if the average deviation of the response to the correct color was below 15 degrees. In case a participant failed, the color sensitivity task was assessed again. In case a participant failed twice, they would be excluded.

The color wheel was created by generating a circle with a radius of 486p that contained 512 successive colors and placing a smaller, background-colored circle with a radius of 362p on top of it. Each color had an angle width of 0.7 degrees (360 degrees divided by 512 colors) and was created with the HSV MATLAB color map. The color wheel was divided into 12 parts, each from which one color was chosen at random to be presented in the center of the color wheel. The orientation of the color wheel was randomized across trials.

After participants responded, a black line appeared that marked and confirmed the response. Additionally, feedback conveying the absolute number of degrees to which the response deviated from the true color (deviance) was given if the deviance was below 10 degrees: e.g. 'Good job! You deviated only 4 degrees!' and by a second black arc that marked the correct location of the color. If the deviance was more than 10 degrees, the feedback only consisted of the second black arc. Participants were instructed to answer precisely, but not to take too much time to respond. There was no maximum response time.

Familiarizing phase (day 1)

Each trial was preceded by a centered black dot for 500ms, signaling the start of a new trial. On each trial, colored squares were presented in the middle of the screen, with the letter 'M' for 'memorize' in the middle (Figure 5.1). During this encoding phase, participants had 500ms to remember the colors of the squares, after which there was a delay of 2000ms during which a fixation cross was shown. During a subsequent interference phase, a new set of colored squares appeared on screen, with one of two letters in the center. 'I' for 'ignore': participants had to ignore the new squares while still remembering the old set of squares; 'U' or 'update': participants now had to remember the new set of squares and forget the old squares. This new set of squares

remained on screen for 500ms, followed by a second delay phase. Dependent on the task-type, distractor resistance (ignore) or flexible updating (update), this delay lasted either 2000ms or 4500ms, respectively, in order to match the time interval between the relevant stimuli (encoding phase for the ignore condition and interference phase for the update condition) and the probe phase. During this probe phase, a color wheel appeared in the center of the screen together with one highlighted frame that indicated the location of the color that should be reported. Participants had 4000ms to indicate the color of this target location by clicking on the corresponding color on the color wheel. When a response was made, a black line appeared on the color wheel at the location where the mouse click was made, remaining on screen until 4000ms had passed since the appearance of the color wheel. Importantly, this means that no advantage can be gained from quick responding in terms of number of trials or potential rewards. No feedback was given on accuracy. If participants did not respond within 4000ms, a message was presented for 500ms in the center of the screen: 'Please respond faster!' Participants were instructed to always keep their eyes fixed on the center of the screen during the entire task.

The number of squares (set size) ranged from 1 to 4 squares. All combinations of set size (ranging from 1-4) and task type (ignore or update) were repeated 8 times, which resulted in 64 trials. Sixteen practice trials preceded those 64 trials. On these practice trials, feedback conveying the deviance was given if the deviance was below 10 degrees: e.g. 'Good job! You deviated only 4 degrees!' and by a second black line that marked the correct location of the color. If the deviance was more than 10 degrees, the feedback only consisted of the second black line. Feedback duration was 700ms. The total duration of the task was 12 minutes.

The colors that were presented during the encoding phase of ignore trials were the same as the colors that were presented during the interference phase of update trials and vice versa. The target colors were the same for both task types. The locations of the squares were allocated equally across trials and the location of the target square was balanced across conditions. The orientation of the color wheel was randomized across trials. Trial order was the same for each participant.

Main phase (day 2)

During the main phase of the color wheel working memory task, performed on the second day, a reward cue was introduced at the beginning of each trial. On half of the trials, participants could win 1 cent, on the other half they could win 10 cents. These rewards on offer were counterbalanced across conditions and remained on screen for 1000ms (Figure 5.1). The task consisted of 128 trials, divided over two blocks. Sixteen

practice trials preceded those 128 trials. The total duration of the task was 28 minutes. To increase the likelihood that participants would receive a bonus on an equal number of trials, they would win the reward, as instructed, if their accuracy on that trial would be equal to or better than their median accuracy on the first day, calculated for each of the 8 task type and set size combinations separately (Table 5.1). Feedback about the achieved reward up to that point was given after every 8 trials and remained on screen for 1500ms: 'Your reward now totals €2.61.' Trial order was randomized across participants, while being counterbalanced over task type, set size and reward.

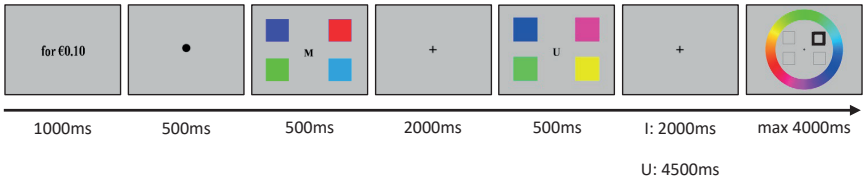

FIGURE 5.1 | Schematic of the color wheel working memory task where participants have to indicate the color of a highlighted target location on the color wheel. I = ignore: participants have to ignore the new squares while still remembering the previous set of squares. U = update: participants have to remember the new set of squares and forget the previous set.

Trait impulsivity

Trait impulsivity was indexed using two widely used self-report questionnaires: 1) the Barratt Impulsiveness Scale (BIS-11), assessing motor, non-planning and cognitive impulsiveness (Patton et al., 1995) and 2) the UPPS Impulsive Behavior Scale (UPPS), which is based on a factor analysis of commonly used impulsivity scales (including the BIS-11) and assesses urgency, (lack of) premeditation, (lack of) perseverance, and sensation seeking (Whiteside & Lynam, 2001). Participants filled in one questionnaire on the first day and the other questionnaire on the second day in a counterbalanced fashion. A Pearson's correlation revealed that total scores on these scales are strongly correlated (r = 0.74, p = 5.0e^{-8}).

Data analysis

Our main dependent variable was mean deviance, but we also explored mean response time and the percentage of trials on which participants received a reward. Outliers were defined a priori as participants whose mean overall deviance was either more than 3 standard deviations higher than that of the global mean or higher than 90 degrees. However, no participant met these exclusion criteria. We ran repeated measures analyses of variance (rmANOVAs) for the two measures of trait impulsivity separately, with the within-subjects factors reward (low, high), task type (ignore, update) and

set size (1-4) and mean-centered trait impulsivity (UPPS-P or BIS-11) as a between-subjects variable. The analyses were performed using the ezANOVA function from the ez package (Lawrence, 2016) in R (version 3.4.2). When the assumption of sphericity was violated, we report Greenhouse-Geisser corrected p-values. We adjusted our alpha-value to 0.025 (Bonferroni-corrected) to account for the two measures of trait impulsivity.

Additionally, we ran a repeated measures correlation to assess a potential speed-accuracy trade-off between deviance and response time using the rmcorr package in R (Bakdash & Marusich, 2018).

Table 5.1 | Mean, standard deviation (SD) and minimum (min) and maximum (max) mean absolute deviance (degrees) on session 1 and percentage of trials on which participants' deviance was below their median deviance on session 1 and therefore received a reward.

	IGNORE					UPDATE				
SET SIZE	**mean**	**SD**	**min**	**max**	**% correct**	**mean**	**SD**	**min**	**max**	**% correct**
1	13.4	16.6	2.7	112.2	49.9	10.2	3.8	3.9	18.6	52.8
2	15.8	15.7	2,8	75.2	66.2	7.2	3.2	2.1	13.8	51.1
3	23.1	24.0	5.6	140.3	62.7	12.1	3.9	5.8	22.3	57.1
4	41.7	34.6	5.2	132.1	67.3	20.6	14.9	4.6	58.2	62.9

RESULTS

In line with previous studies using this paradigm (Hofmans et al., 2019; Papadopetraki et al., 2019), participants performed more poorly, as measured with deviance scores for ignore than update ($F(_{1, 38}$ = 23.4, p = 2.2e^{-5}) and for higher set sizes ($F_{(3, 114)}$ = 46.7, p = 1.6e^{-13}). The difference between ignore and update was larger for higher set sizes ($F_{(3, 114)}$ = 6.0, p = 0.002; Figure 5.2A). There was no main effect of reward ($F_{(1, 38)}$ = 1.7, p = 0.194). Crucially, there was no interaction between reward and task type ($F_{(1, 38)}$ = 0.6, p = 0.446) or between reward, task type and impulsivity (reward x task type x BIS-11: $F_{(1, 38)}$ = 0.1, p = 0.803; reward x task type x UPPS: $F_{(1, 38)}$ = 1.9, p = 0.181). A marginal interaction between reward and BIS-11 (but not UPPS) scores was below our statistical threshold (BIS-11: $F_{(1, 38)}$ = 3.7, p = 0.063; UPPS: $F_{(1, 38)}$ = 2.4, p = 0.131), and was due to reward tending to reduce deviance (i.e. improve accuracy) particularly for participants with higher BIS-11 scores (r = 0.30, p = 0.064). The main effect of impulsivity (BIS-11: $F_{(1, 38)}$ = 0.5, p = 0.499; UPPS: $F_{(1, 38)}$ = 0.005, p = 0.946) was not significant.

Exploratory analyses of response times revealed main effects of task type ($F_{(1, 38)}$ = 14.5, p = 4.9e^{-4}) and set size ($F_{(3, 114)}$ = 45.8, p = 1.7e^{-19}). Participants were slower on update versus ignore trials and slower with increasing set sizes (Figure 5.2B). The interaction between task type and set size was not significant ($F_{(3, 114)}$ = 0.4, p = 0.766). Across participants, reward slowed responding on the task ($F_{(1, 38)}$ = 13.6, p = 7.1e-4). The interaction between reward and task type was not significant ($F_{(1, 38)}$ = 0.4, p = 0.540). However, the interaction between reward, task type and impulsivity was significant using the UPPS score ($F_{(1, 38)}$ = 6.8, p = 0.013). Post-hoc tests revealed that the interaction between reward and UPPS was only present for update ($F_{(1, 38)}$ = 7.5, p = 0.009) and not for ignore ($F_{(1, 38)}$ = 0.1, p = 0.771), such that for update trials, higher trait impulsivity as indexed by UPPS score predicted less reward-related slowing (Figure 5.3). A median split on UPPS scores demonstrated that for ignore trials, both low and high UPPS scores predicted slower responding after the promise of a high reward (low UPPS: $t_{(19)}$ = 2.75, p = 0.013; high UPPS: $t_{(19)}$ = 1.83, p = 0.083). However, for update trials, low UPPS scores predicted slower responding after the promise of a high reward ($t_{(19)}$ = 3.86, p = 0.001), whereas high UPPS scores did not ($t_{(19)}$ = 0.96, p = 0.348). This interaction between reward and task type – the reward effect for update trials minus the reward effect for ignore trials – on response time did not correlate with the interaction between reward and task type on deviance (r = -0.02, p = 0.902). However, across all trials, irrespective of reward or task type, there was a positive within-subjects correlation between response time and deviance (r = 0.15, p = 3.2e^{-28}), indicating that subjects exhibited poorer accuracy when they responded more slowly.

The parallel interaction between reward, task type and impulsivity (in the same direction) did not reach significance for BIS-11 ($F_{(1, 38)}$ = 2.9, p = 0.095). There was no main effect of impulsivity on reaction times (BIS-11: $F_{(1, 38)}$ = 0.1, p = 0.721; UPPS: F(1, 38) = 1.5, p = 0.228).

Exploratory analyses of the percentage of trials on which participants received a reward also did not reveal an interaction between reward and task type ($F_{(1, 38)}$ = 0.6, p = 0.430) or between reward, task type and impulsivity (BIS-11: $F_{(1, 38)}$ = 0.2, p = 0.688; UPPS: $F_{(1, 38)}$ = 0.02, p = 0.880).

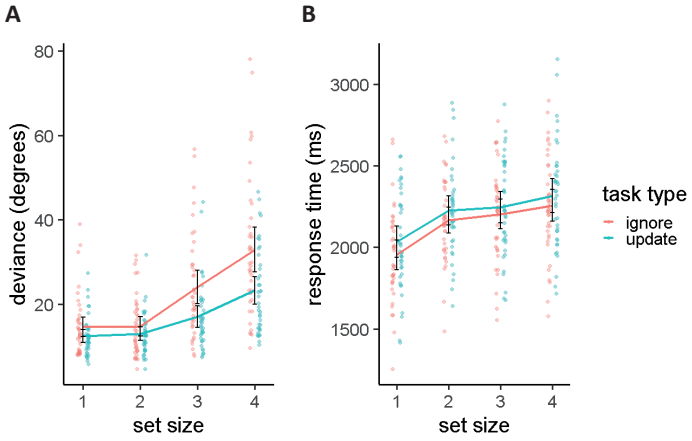

FIGURE 5.2 | A – mean absolute deviance and B – mean response time as a function of set size, separately for each task type. Dots represent mean scores per individual. Error bars represent 95% confidence interval.

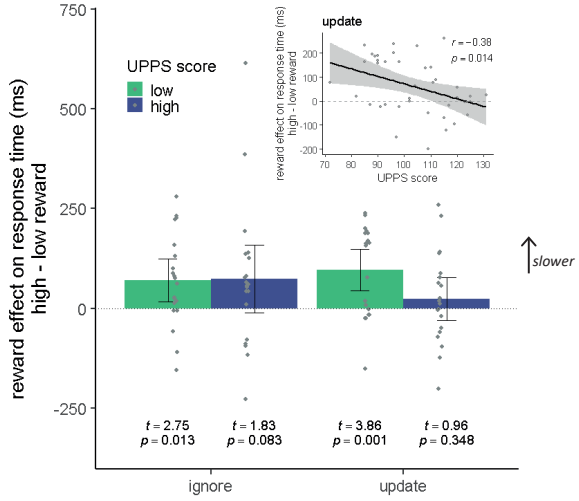

FIGURE 5.3 | Reward effect (high minus low reward) on response time as a function of task type and trait impulsivity (median split on UPPS score). Error bars represent 95% confidence interval. Inset: correlation between trait impulsivity (UPPS score) and the effect of reward on response time for update trials only. Shaded area represents 95% confidence interval.

DISCUSSION

The present study tested the hypothesis that reward motivation has contrasting effects as a function of task demands for flexibility versus stability (Aarts et al., 2011). This was based on our understanding of dopamine's contrasting effects on cognitive flexibility versus stability. Specifically, striatal dopamine has previously been demonstrated to improve performance on tasks requiring cognitive flexibility, but to impair performance on tasks requiring cognitive stability (Cools et al., 2010; Mehta et al., 2001, 2004). Reward cues are well established to elicit dopamine release in the striatum (Howe et al., 2013; Schultz, 1997). Accordingly, we anticipated that the promise of high versus low reward would improve performance on the update task but impair performance on the well matched ignore task condition. Contrary to this hypothesis, we did not find differential effects of reward on task accuracy for distractor resistance versus flexible updating.

However, exploratory analyses did reveal that reward effects on response times depended on both task demands and trait impulsivity. Low impulsive individuals became slower in response to a high reward cue, independent of task demands, but high impulsive individuals only became slower on ignore trials, not on update trials. The interpretation of response times is uncertain in this context. Participants were instructed that they would receive the reward if their deviance was small enough, as long as they responded within the very tolerant response window of 4 seconds. Therefore, they might well have responded more slowly to increase their accuracy. However, in contrast to this speed-accuracy account, slower response times were actually associated with lower accuracy. Therefore, we cautiously interpret the observation that reward-related slowing was reduced on update versus ignore trials in high impulsive individuals to be consistent with our hypothesis that reward motivation increases cognitive flexibility versus stability. Clearly this requires replication in future work and further analyses using for example drift diffusion models to assess whether slower response times reflect an increased decision threshold (i.e. enhanced caution) or a slower rate of evidence accumulation (i.e. poorer memory representation).

One limitation of the current study is that we cannot determine the locus of neural action of our reward manipulation. Our exploratory finding generally concurs with evidence from previous neurocomputational modeling work, according to which increases in striatal dopamine reduces the threshold for (cognitive) action gating by changing the balance between the activating 'go' pathway and the inhibiting 'no-go' pathway (Collins & Frank, 2014; Frank et al., 2001; Frank & O'Reilly, 2006; Hazy et al., 2007). This raises the hypothesis that reward-related changes in the balance between updating and ignoring in the current task are accompanied by changes in striatal BOLD

signaling. Such future work might disentangle this hypothesis from the alternative hypothesis that prospective rewards elicit changes in cognitive control by increasing dopamine in the prefrontal cortex, thus altering the signal-to-noise of current memory representations, with higher signal-to-noise lowering susceptibility to distraction and thus improving performance on ignore relative to update (Braver & Cohen, 2000; Durstewitz & Seamans, 2008; Pessoa, 2017).

At first sight, the present finding might appear at odds with findings from a previous study employing a similar paradigm that distinguished reward effects on ignore and update trials (Fallon & Cools, 2014). This study showed that an unexpected gain relative to an unexpected loss strengthened connectivity between the ventral striatum and prefrontal regions during ignore, suggesting increased recruitment of the distractor resistance network. Although there were no behavioral effects of rewards in this study, reward-related BOLD signaling in the ventral striatum and prefrontal regions was associated with greater accuracy on ignore versus update trials. A key difference between the current paradigm and the one employed in Fallon and Cools (2014) is that rewards were presented as incentive cues in the current study, signaling the promise of reward contingent on good performance, but as unexpected outcomes of a gamble game, signaling the receipt of non-contingent reward in the previous study. Future work is needed to asses potentially different consequences of reward anticipation and receipt for cognitive control (Aarts et al., 2010), particularly given that the control of preparatory and consummatory responses to reward implicate dissociable neural mechanisms (Baldo & Kelley, 2007; Robbins & Everitt, 1992).

It is important to be cautious of false positives and to not overinterpret the current results. The interaction of interest between reward and task type was only present in our exploratory outcome measure response time, of which the interpretation might be ambiguous. Moreover, the interactions with trait impulsivity depended on the questionnaire that was used, questioning the robustness of the results. Nevertheless, these initial results provide an interesting starting point for replication and further testing using neuroimaging methods.

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CHAPTER 6

The cognitive effects of a promised bonus do not depend on dopamine synthesis capacity

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Abstract

Reward motivation is known to enhance cognitive control. However, detrimental effects have also been observed, which have been attributed to overdosing of already high baseline dopamine levels by further dopamine increases elicited by reward cues. Aarts et al. (2014) indeed demonstrated, in 14 individuals, that reward effects depended on striatal dopamine synthesis capacity, measured with [^{18}F]FMT-PET: promised reward improved Stroop control in low-dopamine individuals, while impairing it in high-dopamine individuals. Here, we aimed to assess this same effect in 44 new participants, who had previously undergone an [^{18}F]DOPA-PET scan to quantify dopamine synthesis capacity. This sample performed the exact same rewarded Stroop paradigm as in the prior study. However, we did not find any correlation between reward effects on cognitive control and striatal dopamine synthesis capacity. Critical differences between the radiotracers [^{18}F]DOPA and [^{18}F]FMT are discussed, as the discrepancy between the current and our previous findings might reflect the use of the potentially less sensitive [^{18}F]DOPA radiotracer in the current study.

Introduction

Incentive motivation, or motivation activated by external reward cues, is generally thought to enhance cognitive control (Krawczyk et al., 2007; Pessoa & Engelmann, 2010) and performance-contingent rewards are common across various domains of our society, including sports, education and the workplace. However, negative effects of rewards on cognitive control have also been observed (Aarts et al., 2010, 2011; Ariely et al., 2009; Chib et al., 2012, 2014; Mobbs et al., 2009; Zedelius et al., 2011). For example, it has been demonstrated that when participants received performance-contingent payment for completing various tasks – including tasks that drew primarily on motor skills, memory and creativity – high reward levels had detrimental effects on performance, compared with low and medium reward levels (Ariely et al., 2009). The authors argued that high reward levels can shift arousal or motivation levels beyond the optimal level for executing a task, leading to performance decrements, an effect known as choking. However, not everyone chokes under high reward conditions and to gain more insight into this individual variation we must unravel the neural mechanisms underlying these choking effects. Motivational effects have long been associated with striatal dopamine signaling (Mohebi et al., 2019; Robbins & Everitt, 2007; Salamone et al., 2016) and prior work indeed suggested that individual variation in the effects of motivation on cognitive control depends on dopamine-related functioning, such as dopamine cell loss in Parkinson's disease, midbrain and striatal BOLD activity, loss aversion and dopamine transporter genotype (Aarts et al., 2010, 2012; Chib et al., 2012, 2014; Mobbs et al., 2009; van Holstein et al., 2011). Detrimental effects of rewards resonate with the notion of a potential overdosing of the dopamine system: Rewards, eliciting dopamine release (Schultz, 1997), could have beneficial effects in individuals with low dopamine levels by inducing a shift from sub-optimal to optimal dopamine levels, but detrimental effects in individuals with already high dopamine levels by inducing a shift from optimal to supra-optimal dopamine levels (Cools & D'Esposito, 2011). Building on this work, our previous study (Aarts et al., 2014) directly addressed this issue by assessing the effect of reward on cognitive control as a function of dopamine synthesis capacity, measured with 6-[^{18}F]-fluoro-L-m-tyrosine ([^{18}F]FMT) positron emission tomography (PET). Specifically, participants performed a Stroop task after being promised either a high or a low monetary reward upon successful completion of the task. These monetary incentives were demonstrated to enhance Stroop interference control in participants with low baseline dopamine synthesis capacity in the left caudate nucleus, but impair Stroop interference control in participants with high baseline dopamine synthesis capacity in the left caudate nucleus. This study thus advanced our understanding of differential effects of incentives on cognitive control, by demonstrating that incentive motivation can shift dopamine levels to supra-optimal in participants with already high dopamine levels. It is of note that this effect was present only when participants were

uninformed (i.e., un-cued) about the congruency of the upcoming Stroop target and not when Stroop targets were preceded by cues informing subjects about their congruency.

The finding that a negative correlation between reward effects and dopamine synthesis capacity was present specifically in the left caudate nucleus strengthened evidence from two other prior studies, implicating specifically the left caudate nucleus in the effects of the dopamine transporter gene DAT1 during rewarded cognitive control (Aarts et al., 2010, 2015). Moreover, this finding generally concurred with evidence from an fMRI study demonstrating enhanced connectivity between the ventral striatum and left caudate nucleus when cognitive demand for reward was high (Schmidt et al., 2012). The focus of the effect on the caudate nucleus also converged with functional MRI work from a third research group demonstrating a modulation by reward incentives of specifically the caudate nucleus during (oculomotor) control (Harsay et al., 2011). Finally, confidence in a negative correlation between individual differences in baseline dopamine levels and reward effects on cognitive control was further increased following a subsequent study in Parkinson's disease patients, revealing greater beneficial effects of reward on cognitive control in patients with greater dopamine cell loss, measured with CIT-SPECT (Aarts et al., 2012).

However, the sample size (n = 14) of the key PET study providing the direct evidence for baseline-dependency of reward effects on cognitive control in healthy volunteers was very small for a between-subject correlational design. Such a small sample size is associated not only with low positive predictive value (Heston & King, 2017), but also with high likelihood that effect sizes are biased and overestimated (Button et al., 2013). Therefore, we here aimed to test the effect found by Aarts et al. using a new, larger participant sample, who had already, as part of a previous study, undergone a PET scan with the radiotracer [^{18}F]fluoro-3,4-dihydroxyphenyl-L-alanine ([^{18}F]FDOPA). Specifically, we hypothesized that the effect of anticipated reward on Stroop interference control depends on individual differences in baseline dopamine synthesis capacity in the left caudate nucleus. We supplemented the analyses with voxel-wise correlations of the behavioral measures with dopamine synthesis capacity. Critically, striatal dopamine synthesis capacity in this new sample had already been indexed in the context of a previous study not reported here (www.trialregister.nl/trial/5959; data of which were previously included in Westbrook et al. (Westbrook et al., 2020) and Hofmans et al. (Hofmans et al., 2020)), using [^{18}F]DOPA PET. This is unlike the original study, in which [^{18}F]FMT PET was used to index striatal dopamine synthesis capacity. While [^{18}F]DOPA PET is considered less sensitive than [^{18}F]FMT PET, due to increased background noise and cell clearance of radiolabeled metabolites, we anticipated that a strong association between striatal dopamine synthesis capacity and motivational effects on cognitive control should surface also with [^{18}F]DOPA PET.

The present attempt at conceptual replication was driven by our goal to increase our confidence in the role of dopamine synthesis capacity in motivated cognitive control and is of particular interest because a robust mechanistic account of the link between incentive motivation and cognitive control will advance our understanding of who chokes under high reward conditions and why (Silston & Mobbs, 2014), a topic of great societal relevance today. A preregistration of this study, data and code are available via https://osf.io/ky9s2/.

Materials and methods

Participants

Forty-five (out of a total of 94) right-handed and native Dutch-speaking volunteers who had participated in a previous [^{18}F]DOPA PET study (protocol NL57538.091.16; trial register NTR6140, www.trialregister.nl/trial/5959) accepted the invitation to participate in the current study. All participants gave written informed consent according to the declaration of Helsinki and the experiment was conducted in compliance with and was approved by the local ethics committee (CMO Arnhem-Nijmegen, The Netherlands; Imaging Human Cognition, CMO 2014/288, version 2.2). One dataset was excluded due to an error rate above 33% (36%; mean (SD) = 18 (7) %). With the resulting 44 participants (aged: 19-45 years, mean (SD) = 24 (5.8); 22 women) we adhered to Simonsohn's (2015) recommendation to obtain a sample size at least 2.5 times larger than the original sample size (N = 14). The new sample had 90% power (Faul et al., 2009) to detect a correlation of r = 0.55, which is considerably lower than the correlation of r = 0.75 reported in the original study (two-sided α = 0.0042, see Data analysis). The time between the PET scan and this behavioral study ranged between 0.3 and 1.8 years (mean (SD) = 1.0 (0.4)), which is substantially shorter than in the original study (range: 1.0-4.2 years, mean (SD) = 2.3 (1.1)). Background neuropsychological tests (listening span and behavioral inhibition / activation) had been assessed in the prior [^{18}F]DOPA PET study.

TABLE 6.1 | Demographic, background and task characteristics of participants included in the behavioral analyses.

	Characteristic	Aarts et al. (2014)	Current study	Welch's T	*p*
Demographics	Included participants	14	44		
	Sex (women)	57%	50%		
		Mean (SD)	**Mean (SD)**		
	Age (years)	28 (2.7)	24 (5.9)	-3.4	0.001
	Time between PET and behavioral testing (years)	2.3 (1.1)	1.0 (0.4)	-4.4	0.0006
	Total money obtained	9.33 (0.67) USD	9.31 (0.95) EUR	-0.1	0.922
Neuropsychological assessment	Listening span				
	Total span	3.8 (0.9)[1]	4.3 (1.5)	1.6	0.109
	Total words correct	54.3 (7.7)[1]	59.1 (16.0)	1.5	0.143
	BIS/BAS				
	BIS	19.5 (3.3)	17.6 (4.3)	-1.8	0.087
	BAS (total score)	37.4 (9.9)	39.4 (4.2)	0.76	0.457
Stroop task performance	Overall error rate (%)	15 (6)	17 (7)	1.0	0.319
	Overall response time (ms)	398 (33)	347 (57)	-4.1	0.0002
	Reward effect on Stroop interference on uninformed trials[2]	0.1 (36.0)	-3.2 (32.3)	-0.3	0.767

Neuropsychological assessment included the listening span task (Daneman & Carpenter, 1980) and the Behavioral Inhibition Scale/Behavioral Activation Scale (BIS/BAS; (Carver & White, 1994)). [1]1 missing value; [2]average RT incongruent trials minus average RT congruent trials.

Behavioral paradigm

Participants completed the exact same paradigm as in Aarts et al.: a rewarded word-arrow Stroop paradigm, where they responded with a left or right button press to the words "left" or "right" in a left or right pointing arrow, using their right index finger or right middle finger, respectively (Figure 6.1a). The direction indicated by the word could either be congruent (same direction as the arrow) or incongruent (opposite direction). Each trial was preceded by a reward cue for a duration of 1-2 seconds, which indicated either a high (15 cents) or low (1 cent) reward that would be earned on that trial if the participant responded correctly and within the response window. After the reward cue, an information cue was shown on the screen for 1-2 seconds which was either informative, in which case it announced to the participant whether the trial would be congruent (green circle) or incongruent (red cross), or uninformative, in which case it showed a question mark. The information cues were added in the original study to assess potential anticipatory reward effects on proactive control, i.e. the ability to prepare for the upcoming congruent and incongruent Stroop targets (without being able to prepare a left or right motor response). Reward cues, information cues and congruency were equally divided across 240 trials, which lasted about 30 minutes.

As in the original study, before the actual task, participants completed 3 practice blocks. The first one to familiarize them with the information cues (12 trials), the second one to familiarize them with the reward cues (32 trials), and a third one - similar to the actual experiment - to set the initial response windows for the different trial types (48 trials). The initial response windows were set as the average response time per trial type (high or low reward; informed or uninformed; congruent or incongruent). During the actual experiment, the response windows were adapted after correct responses within the time window (-25 ms) or too late responses (+25 ms). After every block of 30 trials participants received feedback on their performance, showing their obtained reward on that block, the maximum reward that could have been obtained, their misses (too late), their errors (in time but wrong) and their reward for the total experiment so far, which remained on screen for 15 seconds. Due to the dynamic response windows, obtained reward was similar across participants and trial types (mean (SD) = €9.31 (0.95) for the entire experiment). The task was performed on a computer running on Windows 7 and a screen resolution of 1920x1080p, and the stimuli were shown using Presentation (version 20.2, 2018).

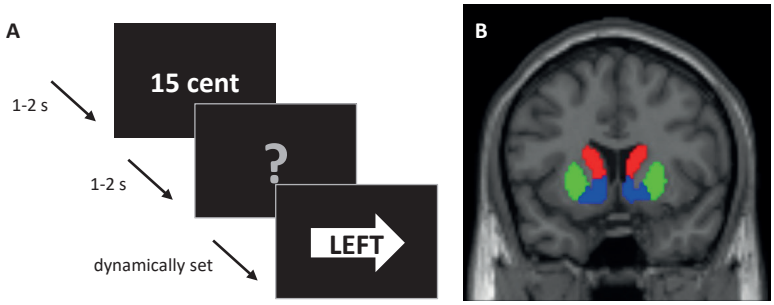

FIGURE 6.1 | Schematic of data acquisition. (a) Schematic of an example word-arrow Stroop trial. Participants could either earn a high (15 cents) or low (1 cent) reward for a correct answer within the response window, which was cued at the start of the trial (1-2 seconds). After that, an information cue was presented for 1-2 seconds, indicating a congruent (green circle) or incongruent (red cross) trial, or giving no information about the upcoming congruency (grey question mark). Upon seeing the word-arrow Stroop target, participants had to respond to the word with a left or right button-press within the dynamically set response window. (b) Coronal view of our regions of interest including the bilateral caudate nucleus (red), putamen (green) and ventral striatum (blue).

PET acquisition

PET scans were carried out at the Department of Nuclear Medicine of the Radboud university medical center, using a Siemens PET/CT scanner and the radiotracer [^{18}F] DOPA. Participants received 150 mg of carbidopa and 400 mg of entacapone 50 minutes before scanning, to minimize peripheral metabolism of [^{18}F]DOPA and thereby

increase central [^{18}F]DOPA availability. The procedure started with a low dose CT scan (approximately 0.75 mCi) followed by a bolus injection of [^{18}F]DOPA into an antecubital vein and an 89 minute dynamic PET scan (approximately 5 mCi). The data were divided into 24 frames (4x1, 3x2, 3x3, 14x5 min) and reconstructed with weighted attenuation correction and time-of-flight recovery, scatter corrected, and smoothed with a 3 mm full-width-at-half-maximum (FWHM) kernel.

Structural MRI

A high-resolution anatomical scan, T1-weighted MP-RAGE sequence (repetition time = 2300 ms, echo time = 3.03 ms, 192 sagittal slices, field of view = 256 mm, voxel size 1 mm isometric) was acquired using a Siemens 3T MR scanner with a 64-channel coil. These were used for coregistration and spatial normalization of the PET scans.

PET analysis

PET data were preprocessed and analyzed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). All frames were realigned for motion correction and coregistered to the anatomical MRI-scan, using the mean PET image of the first 11 frames. Dopamine synthesis capacity was computed as the [^{18}F]DOPA influx constant per minute (K_i) per voxel relative to the grey matter of the cerebellum, using Gjedde-Patlak graphical analysis (Patlak et al., 1983). The individual cerebellum grey matter masks were obtained by segmenting the individuals' anatomical MRI scan, using Freesurfer (https://surfer.nmr.mgh.harvard.edu/). The K_i values were calculated based on the PET frames from the 24th to 89th minute. We then extracted average K_i values from six regions of interest (ROIs) – left and right caudate nucleus, putamen and ventral striatum – defined using masks based on an independent functional connectivity-analysis of the striatum (Piray et al., 2017) (Figure 6.1b). These ROIs are different from the ROIs used by Aarts et al. (Aarts et al., 2014), which were specified according to guidelines described by Mawlawi et al. (Mawlawi et al., 2001). An overlay of the two sets of ROIs are displayed in Supplementary Figure S6.1. Supplementary analyses reveal a high Pearson correlation coefficient between the mean K_i values extracted from the two sets of ROIs (all $r > 0.96$). Analyses assessing the relationship between dopamine synthesis capacity in the left caudate nucleus as specified according to Mawlawi et al. and the effect of reward on Stroop interference can be found in the Supplementary information, including Supplementary Figure S6.2). For voxel-wise group analyses, the K_i maps were normalized to MNI space and smoothed using an 8 mm FWHM kernel.

Data analysis

We expected a linear relationship between dopamine synthesis capacity and the effect of reward on Stroop interference. This prediction derives from the hypothesis that there is a negative quadratic relationship between dopamine signaling and cognitive performance (Cools & D'Esposito, 2011), such that both too little and too much dopamine is detrimental for performance: in low-dopamine participants, a putative increase in dopamine release in response to the promise of reward will positively affect performance by shifting dopamine levels from suboptimal to optimal. Conversely, in high-dopamine participants, the same reward promise will negatively affect performance by shifting dopamine levels from optimal to supra-optimal. See Supplementary Figure S6.3 and S6.4 for an exploration of nonlinear relationships between dopamine signaling and cognitive performance.

The main effect of interest was the correlation between the effect of reward on Stroop interference (in terms of response times) on uninformed trials and dopamine synthesis capacity in the left caudate nucleus, as was observed in the original study. For completeness, we also explored the other five ROIs. We analyzed response times (RTs) of all correct trials, including trials on which participants were "too late", and error rates. Participants with error rates above 33% were excluded. We ran separate repeated measures analyses of variance (rmANOVA) for each region of interest and two dependent variables: Stroop interference on RT and on error rate (mean RT or error rate on incongruent trials minus mean RT or error rate on congruent trials). The within-subjects factors were REWARD (low, high) and INFORMATION (uninformed, informed), and [^{18}F]DOPA K_i in the left or right caudate nucleus, putamen, or ventral striatum was a covariate of interest. The analyses were performed using the ezANOVA function from the ez package (Lawrence, 2016) in R (version 3.4.2). We corrected for multiple comparisons (6 ROIs, 2 dependent variables), resulting in a Bonferroni-corrected alpha value of 0.0042. Pearson's correlations were calculated between the K_i values of the six ROIs and the effect of reward on Stroop interference in terms of RT on uninformed trials for comparison with the original study (Aarts et al., 2014). We supplemented the analyses with voxel-wise correlations between the reward effect on Stroop interference and dopamine synthesis capacity within the voxels comprising the entire striatum (the sum of the 6 regions of interest, specified above). Statistical significance was defined as family-wise error corrected $p < 0.05$ at peak coordinate, after small volume correction for all voxels within the striatal region of interest.

Although striatal [^{18}F]DOPA uptake shows high test-retest reliability within a time frame of 2 years (Egerton et al., 2010), we performed additional regression analyses, separately for each of the six ROIs, to assess whether any effects of the interaction

between REWARD and dopamine synthesis capacity on Stroop interference depended on time between the PET scan and the behavioral testing day, while also including age and gender in the model, using the lm function from the stats package in R.

We could not directly compare baseline dopamine synthesis capacity between the original and the current study, because the PET tracer differed between the two studies. However, to appreciate possible differences between the main findings of the current study and that of the original study, it is important to analyze comparability of the sample (Table 6.1). We therefore compared the two samples in terms of age, neuropsychological assessment (listening span and behavioral inhibition / activation) and overall performance in terms of error rates and RT, using Welch's t-tests. We then compared reward effects on Stroop interference in terms of RT between the two studies, with the hypothesis that reward would decrease interference in individuals with lower baseline dopamine synthesis capacity and increase interference in individuals with higher baseline dopamine synthesis capacity (Aarts et al., 2014; Cools & D'Esposito, 2011). We assessed differences in mean using a Welch's t-test and differences in variances using a Levene's test. Moreover, given the well-established link between dopamine and response vigor (Niv et al., 2007; Robbins & Everitt, 2007; Salamone et al., 2016), we assessed the effect of baseline dopamine synthesis capacity on response times, both the main effect and in interaction with reward, in the current and the original study using an rmANOVA (Supplementary Table S6.1, S6.2).

To allow for quantification of evidence for or against our hypotheses, we additionally report Bayesian individual effects analyses performed in JASP (version 0.10.2.0), with default JASP Cauchy priors. The $BF_{inclusion}$ reflects how strongly the data support inclusion of a factor. We performed a sequential Bayesian correlation to illustrate evidence accumulation against the previously found correlation between the effect of reward on Stroop interference and dopamine synthesis capacity in the left caudate nucleus after observing the new data. Data from both studies were included; dopamine synthesis capacity values were separately standardized (z-scored) for both [^{18}F]DOPA and [^{18}F]FMT K_i values.

All continuous independent variables ([^{18}F]DOPA K_i values, time between the PET and behavioral session, overall response times and age) were mean centered.

Results

Participants performed more poorly on incongruent than congruent trials (RT: $F_{(1,43)}$ = 185.3, p = 3.438e^{-17}, BF_{INC} = 3.217e^{+14}; error rate: $F_{(1,43)}$ = 137.7, p = 5.394e^{-15}, BF_{INC} = 6.434e^{+13}), on uninformed than informed trials (RT: $F_{(1,43)}$ = 35.0, p = 4.829e-7, BF_{INC} = 3.217e^{+14}; error rate: $F_{(1,43)}$ = 34.1, p = 6.224e^{-7}, BF_{INC} = 4.949e^{+13}) and low reward than high reward trials (RT: $F_{(1,43)}$ = 14.2, p = 4.974e^{-4}, BF_{INC} = 3.217e^{+14}; error rate: $F_{(1,43}$) = 0.2, p = 0.662, BF_{INC} = 4.949e^{+13}). These results validate the task manipulation, and they are similar to findings in the original study.

Crucially, and in contrast with the original study, there was no interaction effect between REWARD, INFORMATION and dopamine synthesis capacity in any of the six ROIs on Stroop interference in terms of response times or error rates (Table 6.2). For completeness, we also report the effect of reward on Stroop interference independent of the factor INFORMATION (Table 6.2). Pearson's correlations between baseline dopamine synthesis capacity and the effect of reward on Stroop interference on uninformed trials only revealed no significant associations (all r < |0.22|, p > 0.158, BF < 0.575; Figure 6.2). Importantly, the 95% confidence interval for the correlation between dopamine synthesis capacity in the left caudate nucleus and the effect of reward on Stroop interference in the present study (r = -0.06, p = 0.700, 95% CI [-0.35, 0.24]) did not overlap with that of the originally reported effect of r = 0.75. Upon visual inspection of Figure 6.2, we additionally explored a quadratic relationship between dopamine synthesis capacity in the left and right caudate nucleus and the effect of motivation on Stroop interference in terms of RT on uninformed trials, but did this not yield significant results (Supplementary information). Moreover, a supplementary rmANOVA and Pearson's correlation analysis revealed no relationship between dopamine synthesis capacity in the left caudate nucleus as specified according to Mawlawi et al. (Mawlawi et al., 2001) and used in Aarts et al. (Aarts et al., 2014) and the effect of reward on Stroop interference (Supplementary Figure S6.2).

TABLE 6.2 | Interaction effects in terms of response times (RT) and error rates obtained from the rmANOVAs with dopamine synthesis capacity in each ROI as a single covariate. The dependent variable is Stroop performance (mean RT or error rate on incongruent trials minus mean RT or error rate on congruent trials). Effect in dark purple was the interaction observed in Aarts et al. to be significant.

	Reward x information x DAsynth			Reward x DAsynth		
	$F_{(1,42)}$	*p*	BF_{INC}	$F_{(1,42)}$	*p*	BF_{INC}
RT						
Left caudate nucleus	**1.9**	**0.177**	**0.003**	0.5	0.473	0.044
Right caudate nucleus	0.6	0.456	0.003	1.4	0.244	0.041
Left putamen	2.4	0.126	0.003	0.2	0.628	0.029
Right putamen	3.4	0.072	0.004	0.3	0.612	0.029
Left ventral striatum	1.5	0.234	0.003	0.4	0.546	0.030
Right ventral striatum	0.8	0.365	0.002	0.0	0.964	0.034
Error rate						
Left caudate nucleus	0.5	0.492	0.003	0.4	0.526	0.041
Right caudate nucleus	0.3	0.600	0.017	0.2	0.623	0.065
Left putamen	0.2	0.658	0.018	0.0	0.946	0.068
Right putamen	0.7	0.417	0.019	0.2	0.666	0.076
Left ventral striatum	0.0	0.951	0.014	0.3	0.618	0.059
Right ventral striatum	0.3	0.618	0.015	0.0	0.961	0.065

p-values below a Bonferroni-corrected alpha-value of 0.0042 were considered significant.
Note that Aarts et al. analyzed the interaction between congruency, reward, information and dopamine synthesis capacity on response times and error rates. Here, we show the equivalent interaction between reward, information and dopamine synthesis capacity on Stroop interference (i.e. the difference between incongruent and congruent trials).

Voxel-wise analyses of the effect of reward on Stroop interference on uninformed trials confirmed the lack of significant correlations with any of the voxels within the striatum (Figure 6.3). Separate multiple regression analyses for each ROI further confirmed the lack of a significant interaction between REWARD, INFORMATION and dopamine synthesis capacity or between REWARD and dopamine synthesis capacity on Stroop interference in terms of RT or error rate (Table 6.3). Additionally, time between PET and behavioral testing, age and gender did not affect the interaction between REWARD, INFORMATION and dopamine synthesis capacity or the interaction between REWARD and dopamine synthesis capacity on Stroop interference in terms of RT or error rate (Table 6.3). To further illustrate evidence against a correlation between the effect of REWARD on Stroop interference and dopamine synthesis capacity in the left caudate nucleus on uninformed trials, we ran a sequential Bayesian correlation including the data from both the original study and the current study. This revealed a strong increase in evidence in favor of a correlation when including participants from the original study, followed by a strong decline in evidence when including participants from the current study, culminating in moderate evidence against a correlation (Figure 6.4).

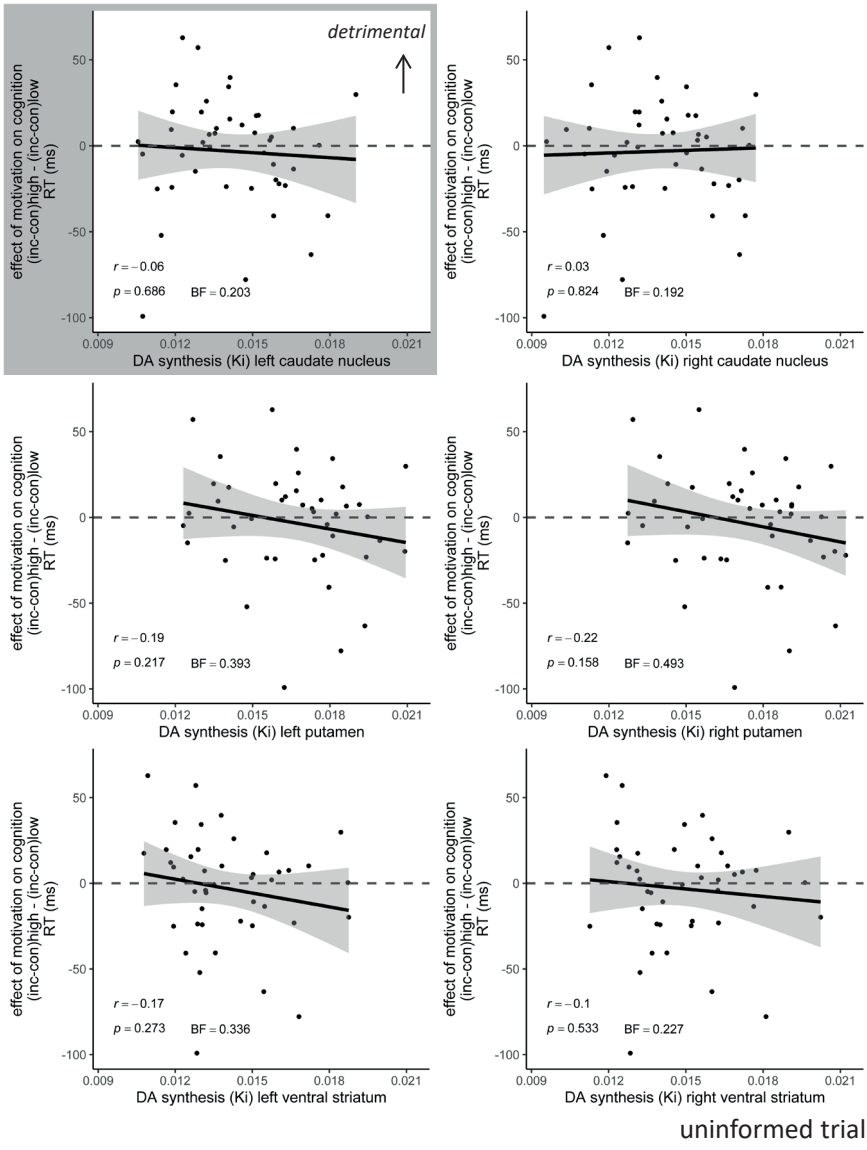

FIGURE 6.2 | The effect of reward on Stroop interference (RT: incongruent – congruent) on uninformed trials plotted as a function of dopamine synthesis capacity in the six ROIs. Shaded area around the regression line represents 95% confidence interval. *N* = 44.; RT (ms) = response time in milliseconds; K_i = [^{18}F]DOPA uptake, reflecting dopamine synthesis capacity. Effect in grey was the correlation observed in Aarts et al. to be significant.

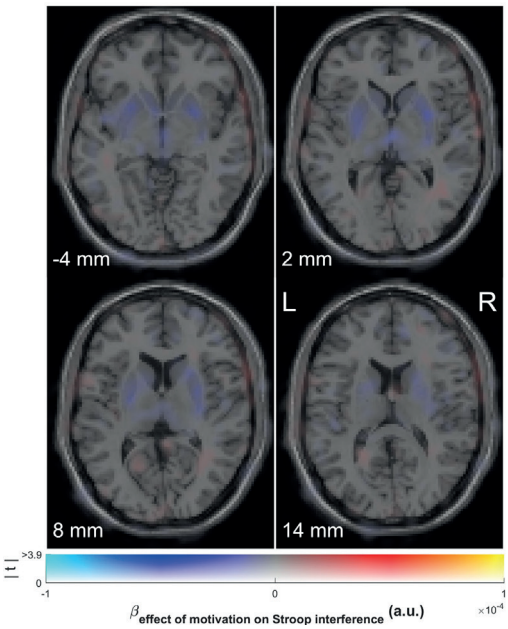

FIGURE 6.3 | Association of baseline dopamine synthesis capacity with the effect of reward on Stroop interference on uninformed trials. Voxels showing a positive (red) or negative (blue) regression coefficient on the effect of a promised reward on Stroop interference in terms of response times on uninformed trials. Dual-coded and simultaneously displaying the contrast estimate (*x* axis) and *t* values (*y* axis). The hue indicates the size of the contrast estimate, and the opacity indicates the height of the *t* value. The *z* coordinates correspond to the standard MNI brain. No voxels survive $p < 0.05$ peak-level corrected (FWE) or $p < 0.001$ uncorrected. Plotted using a procedure introduced by Allen et al. (E. A. Allen et al., 2012) and implemented by Zandbelt (Zandbelt, 2017).

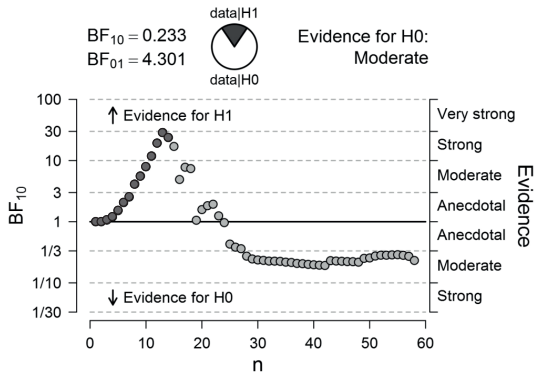

FIGURE 6.4 | Sequential analysis showing progression of the Bayes Factor (BF) as new participants (n) enter the analysis. Values above 1 represent evidence for a correlation between dopamine synthesis capacity in the left caudate nucleus and a motivation effect on Stroop interference on uninformed trials, whereas values below 1 represent evidence against a correlation. Each dot represents the BF after inclusion of the next participant. Dark grey dots represent the 14 participants from Aarts et al. entered first; light grey dots represent the 44 participants from the current study. Order of including participants within each group was at random.

TABLE 6.3 | Interaction effects obtained from multiple linear regression analyses assessing the effect of age, gender and time between the PET scan and behavioral testing (PET_behavioral) on motivational effects on Stroop interference (incongruent trials minus congruent trials) in terms of response times (RT) and error rates. Separate analysis for each ROI.

	Reward x information x DAsynth		Reward x DAsynth		Reward x information x DAsynth x age		Reward x DAsynth x age		Reward x information x DAsynth x gender		Reward x DAsynth x gender		Reward x information x DAsynth x PET_behavioral		Reward x DAsynth x PET_behavioral	
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
RT																
Left caudate nucleus	$-3.4e^{3}$	0.348	$-2.6e^{3}$	0.481	$-3.7e^{2}$	0.118	$-1.2e^{2}$	0.629	$3.3e^{3}$	0.177	$1.8e^{3}$	0.449	5.5	0.592	4.7	0.644
Right caudate nucleus	$-3.6e^{3}$	0.246	$-2.2e^{3}$	0.472	$-2.1e^{2}$	0.283	$-7.9e^{1}$	0.689	$3.2e^{3}$	0.134	$1.4e^{3}$	0.515	1.4	0.880	$-9.3e^{-2}$	0.992
Left putamen	$6.5e^{2}$	0.845	$1.5e^{3}$	0.644	$1.9e^{1}$	0.945	$6.3e^{1}$	0.816	$4.6e^{2}$	0.837	$-4.4e^{2}$	0.844	4.9	0.599	7.1	0.445
Right putamen	$9.8e^{2}$	0.756	$1.6e^{3}$	0.618	$1.3e^{1}$	0.959	$7.4e^{1}$	0.768	$2.5e^{2}$	0.900	$-5.2e^{2}$	0.796	4.0	0.601	5.8	0.442
Left ventral striatum	$-2.0e^{3}$	0.634	$8.6e^{2}$	0.833	$-5.6e^{2}$	0.204	$-2.3e^{1}$	0.959	$1.5e^{3}$	0.588	$-6.5e^{1}$	0.981	$1.3e^{1}$	0.181	$1.2e^{1}$	0.230
Right ventral striatum	$-1.8e^{3}$	0.614	$8.1e^{2}$	0.822	$-5.2e^{2}$	0.082	$-1.4e^{2}$	0.643	$1.4e^{3}$	0.551	$-2.5e^{2}$	0.915	$1.4e^{1}$	0.123	$1.4e^{1}$	0.140
Error rate																
Left caudate nucleus	6.6	0.697	$1.5e^{1}$	0.377	$-5.7e^{-2}$	0.959	$-3.2e^{-1}$	0.776	-3.4	0.767	$-1.1e^{1}$	0.322	$2.1e^{-2}$	0.661	$8.8e^{-3}$	0.855
Right caudate nucleus	$1.1e^{1}$	0.470	$1.2e^{1}$	0.430	$5.4e^{-1}$	0.570	-7.8^{-1}	0.410	-7.6	0.460	-8.0	0.430	$1.1e^{-2}$	0.810	$2.5e^{-2}$	0.580
Left putamen	$6.8e^{-2}$	0.996	$2.5e^{1}$	0.100	$-8.2e^{-1}$	0.513	$2.2e^{-1}$	0.859	-1.9	0.854	$-1.7e^{1}$	0.101	$4.5e^{-4}$	0.992	$-3.6e^{-3}$	0.934
Right putamen	3.4	0.814	$1.9e^{1}$	0.195	$-5.9e^{-1}$	0.608	$3.6e^{-2}$	0.975	-4.8	0.601	$-1.3e^{1}$	0.153	$-7.1e^{-3}$	0.839	$-6.2e^{-3}$	0.860
Left ventral striatum	-1.1	0.955	$1.9e^{1}$	0.316	-1.6	0.431	$4.3e^{-1}$	0.833	-1.7	0.896	$-1.1e^{1}$	0.379	$1.2e^{-3}$	0.979	$-3.8e^{-2}$	0.408
Right ventral striatum	-4.0	0.811	$1.4e^{1}$	0.401	$-9.8e^{-1}$	0.478	$3.9e^{-1}$	0.778	2.3	0.837	-8.6	0.442	$-9.8e^{-3}$	0.820	-2.2^{-2}	0.615

Model: stroop_effect ~ DAsynth x reward x information x age + DAsynth x reward x information x gender + DAsynth x reward x information x PET_behavioral

Average age differed significantly between the original and the current study (original study: mean = 28.1 years old; current study: mean = 24.3 years old; $t_{(47)}$ = -3.4, p = 0.001; Table 6.1). To assess whether this could have caused the lack of effect of interest in the current study, we repeatedly discarded the youngest participant from our current dataset until age no longer differed between the studies, before rerunning the rmANOVAs. This resulted in a dataset including 26 participants (mean age = 26.9 years old; $t_{(37)}$ = -0.9, p = 0.379). However, we did not observe a significant REWARD (by INFORMATION) by dopamine synthesis capacity interaction effect on Stroop interference (Supplementary Table S6.3).

Similarly, individual average RTs across trials differed significantly between the original and the current study (original study: mean = 397.5 ms; current study: mean = 346.9 ms; $t_{(40)}$ = -4.1, p = 2.0e-4; Table 6.1). We therefore repeatedly discarded the fastest participant from our current dataset until the average RTs no longer differed, resulting in a dataset including 29 participants (mean RT = 371.8; $t_{(39)}$ = -1.9, p = 0.064). However, we did not observe a significant REWARD (by INFORMATION) by dopamine synthesis capacity effect on Stroop interference (Supplementary Table S6.4). We additionally ran a multiple linear regression for each ROI including the terms REWARD, INFORMATION, dopamine synthesis capacity and individual average RT across all trials, including all interactions, which confirmed the lack of a significant effect of average RTs (Supplementary Table S6.5).

To establish that the discrepancy between the studies does not reflect differences in the dynamic range of the key variable of interest, we also compared the means and variances of the reward effects on Stroop interference on uninformed trials in terms of RT between the two studies. The two participant samples did not differ significantly from each other in terms of their means and variances (Figure 6.5), as revealed by a Welch's t-test (original study: mean = 0.07 ms; current study: mean = -3.2 ms; $t_{(20)}$ = -0.3, p = 0.767; Table 6.1) and Levene's test ($F_{(1,56)}$ = 0.2, p = 0.660), respectively.

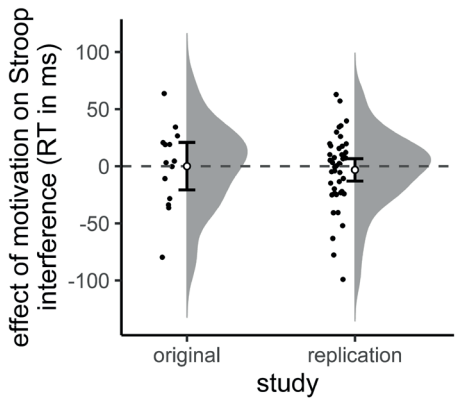

FIGURE 6.5 | The effect of promised reward on Stroop interference (RT incongruent trials minus RT congruent trials) on uninformed trials in the original study (Aarts et al.) and the current replication attempt. Individual data points and probability distribution. Error bars represent 95% confidence interval around the mean. Plotted using R_raincloudS.R (M. Allen et al., 2018).

Discussion

The current study reveals no evidence for an interaction between monetary incentives and dopamine synthesis capacity, indexed with [^{18}F]DOPA PET, on Stroop interference. Bayesian analyses in fact provide evidence in favor of a lack of a relationship between dopamine synthesis capacity and reward effect on Stroop interference. Our conclusion is therefore not consistent with the earlier findings by Aarts et al. (Aarts et al., 2014).

It is possible that the discrepancy between the findings of the two studies reflects the use of [^{18}F]DOPA in the present study, as opposed to [^{18}F]FMT used in the original study. [^{18}F]DOPA is a substrate for catechol-O-methyltransferase (COMT) in the periphery. Metabolites can cross the blood-brain-barrier and will distribute evenly throughout the brain, enhancing background noise relative to the use of [^{18}F]FMT, which is not a substrate for COMT (Becker et al., 2017). However, this is mainly a concern when one is interested in brain areas with low dopamine levels, as opposed to the dopamine-rich striatum. Moreover, entacapone was administered before PET scanning to inhibit peripheral COMT metabolism, further reducing the risk of a too low signal-to-noise ratio. [^{18}F]DOPA and [^{18}F]FMT also differ in their metabolic actions after decarboxylation by aromatic amino acid decarboxylase (AAAD), including higher affinity of [^{18}F] DOPA metabolites compared with [^{18}F]FMT metabolites for the vesicular monoamine transporter, leading to increased cell clearance of radiolabeled [^{18}F]DOPA metabolites (Doudet et al., 1999). Indeed, differences in aging effects on dopamine synthesis capacity measured with [^{18}F]DOPA and [^{18}F]FMT have been observed, possibly owing to age-related changes in post-AADC metabolism (DeJesus et al., 2001). However, this

would mostly be a concern for extended scanning times, as [^{18}F]DOPA behaves as an irreversibly bound tracer in the first 90 minutes after tracer injection, during which their uptake rates are tightly correlated (Becker et al., 2017; Doudet et al., 1999).

Another possibility is that the discrepancy between the original and the current study was introduced by group differences in sample characteristics. However, differences in overall response times and age did not explain the lack of significant effects in the current study. According to the dopamine overdose hypothesis (Cools & D'Esposito, 2011), monetary incentives might enhance Stroop interference control in participants with very low average levels of baseline dopamine, whereas those incentives would impair control in participants with very high average levels. Sampling only participants with intermediate dopamine levels should lead to very small reward effects. However, a comparison of reward effects between the two studies demonstrated similar means and variances within the two samples. We therefore argue that the current result decreases our belief in the previously observed correlation between motivational effects on cognitive control and baseline dopamine synthesis capacity.

Notably, this conclusion would not imply that dopamine transmission is not important for the motivation of cognitive control, because brain dopamine levels are a function not only of dopamine synthesis capacity, but also of other factors, including transporter density, dopamine receptor availability, dopamine release and genetic make-up. Thus, the current study cannot refute hypothesized correlations between motivational effects on cognitive control and other measures of dopamine function. For example, the current design does not disconfirm previously demonstrated and replicated links between motivation, cognitive control and polymorphisms in the dopamine transporter gene (Aarts et al., 2010, 2015; van Holstein et al., 2011), dopamine release (Jonasson et al., 2014) or dopamine-related disease status (Aarts et al., 2012; Manohar et al., 2015; Timmer et al., 2018). Similarly, the current failure to replicate does not undermine other studies demonstrating a link between dopamine synthesis capacity and cognitive motivation indexed with other tasks, such as delay discounting (Smith et al., 2016), cognitive effort discounting (Hofmans et al., 2020; Westbrook et al., 2020) or reward-based reversal learning (Cools et al., 2009). Nevertheless, the presently observed lack of effect reduces our confidence in the link between dopamine synthesis capacity and the effect of a promised reward on Stroop interference and stresses the need for further studies.

Acknowledgments

We thank Lieke van Lieshout and Felix Linsen for assistance during data collection.

Supplementary information

Comparison between the regions of interest used in the current study and the study by Aarts et al

Here we report results from a comparison between the regions of interest (ROIs) used in the current study and those used in the study by Aarts and colleagues (Aarts et al., 2014). In the current study we based our ROIs on functional connectivity analyses (Piray et al., 2017) (see PET analysis in main text), while the ROIs in the study by Aarts and colleagues were drawn according to guidelines described previously by Mawlawi and colleagues (Mawlawi et al., 2001).

The ROIs as used by Aarts et al. were specified in MNI space and transformed to subject native space for analyses. Figure S6.1 displays the two sets of ROIs in MNI space. Both sets of ROIs included the bilateral caudate nucleus (medial caudate region and dorsal caudate nucleus region), putamen (dorsal-anterior and dorsal-posterior putamen region) and ventral striatum (nucleus accumbens, ventral caudate nucleus, and ventral parts of the putamen). A Pearson's correlations revealed that there was a strong positive correlation between the [^{18}F]DOPA K_i values in the two sets of ROIs (native space; left caudate nucleus: $r = 0.97$, $p < 2e^{-16}$; right caudate nucleus: $r = 0.96$, $p < 2e^{-16}$; left putamen: $r = 0.99$, $p < 2e^{-16}$; right putamen: $r = 0.99$, $p < 2e\text{-}16$; left ventral striatum: $r = 0.98$, $p < 2e^{-16}$; right ventral striatum: $r = 0.97$, $p < 2e^{-16}$).

Next we reran the rmANOVAs on the dependent variable Stroop interference – mean RT incongruent trials minus mean RT congruent trials – including the within-subjects factors REWARD (low, high) and INFORMATION (uninformed, informed), and [^{18}F]DOPA K_i in the left dorsal caudate nucleus (as specified according to Mawlawi et al. and used by Aarts et al.) as a covariate of interest. There were no significant interactions between REWARD, INFORMATION and dopamine synthesis capacity ($F_{(1,42)} = 2.2$, $p = 0.150$, $BF_{INC} = 0.003$) or between REWARD and dopamine synthesis capacity (independent of INFORMATION; $F_{(1,42)} = 0.1$, $p = 0.715$, $BF_{INC} = 0.044$). Figure S6.2 shows the correlation between dopamine synthesis capacity in the left dorsal caudate nucleus (as specified according to Mawlawi et al.) and the effect of motivation on Stroop interference on uninformed trials.

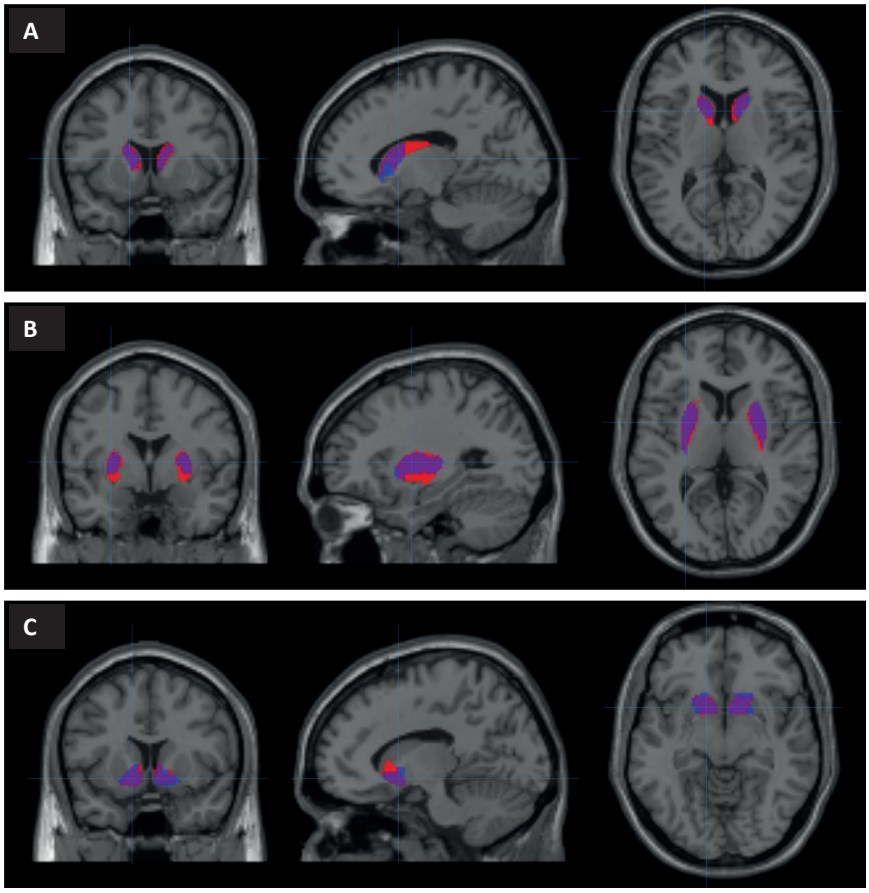

Figure S6.1 | Overlay of the regions of interest (ROIs) used in the current study and in Aarts et al. (Aarts et al., 2014). ROIs used in the current study are displayed in red; ROIs used in Aarts et al. are displayed in blue; overlap is purple. **a** – caudate nucleus with crosshairs at MNI coordinates [-14, 10, 10]. **b** – putamen with crosshairs at MNI coordinates [-28, 0, 6]. **c** – ventral striatum with crosshairs at MNI coordinates [-12, 10, -8].

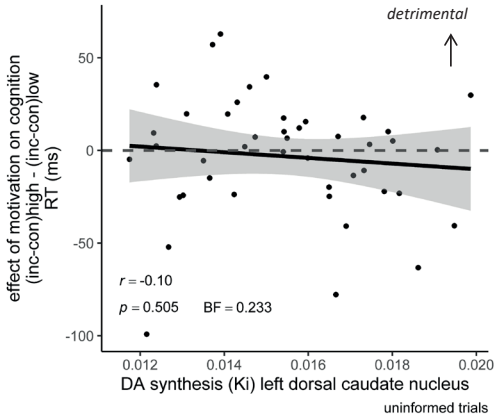

FIGURE S6.2 | The effect of reward on Stroop interference (RT: incongruent – congruent) on uninformed trials plotted as a function of dopamine synthesis capacity in the left dorsal caudate nucleus (ROI specified according to Mawlawi et al. and used by Aarts et al.). Shaded area around the regression line represents 95% confidence interval. RT (ms) = response time in milliseconds; K_i = [^{18}F]DOPA uptake, reflecting dopamine synthesis capacity; *N* = 44.

No evidence for a quadratic relationship between dopamine synthesis capacity and Stroop interference on low reward trials

Our primary hypothesis was that dopamine synthesis capacity would be associated linearly with the effect of reward on Stroop performance. This hypothesis was based on a putative inverted-U shaped relationship between dopamine and Stroop performance, whereby further increases in dopamine elicited by the promise of reward would shift dopamine levels from suboptimal to optimal in low-dopamine participants, but from optimal to supra-optimal in high-dopamine participants. In addition to testing the linear effects of reward, we also explored quadratic effects under low-reward (putative baseline) conditions. To this end, we ran linear regressions (separately for each ROI) in R using the lm function, including the quadratic *z*-scored K_i term as independent variable and Stroop interference on the uninformed low reward trials as dependent variable. A *p*-value below a Bonferroni-corrected alpha-level of 0.0083 (0.05÷6 ROIs) was considered significant. We additionally ran the same Bayesian linear regressions in JASP to obtain a Bayes Factor for the effect. Results are displayed in Figure S6.3. Although this revealed that Stroop interference was indeed strongest for individuals with the lowest and highest dopamine synthesis capacity in the right caudate nucleus (R^2 = 0.159, p = 0.007, BF = 2.99), this relationship was driven by the participant with the highest Stroop interference score, who was an outlier according to a Grubbs' test (G = 4.0, p = 1.6e^{-4}). Without this participant the quadratic relationship was not present anymore (R^2 = 0.03, p = 0.292, BF = 0.481). There were no significant quadratic relationships between dopamine synthesis capacity in the other ROIs and Stroop interference. Crucially, the

quadratic effect between dopamine synthesis capacity (in the left dorsal caudate nucleus, as specified according to Mawlawi et al. (Mawlawi et al., 2001) and Stroop interference was also not present in the study by Aarts and colleagues (Figure S6.4).

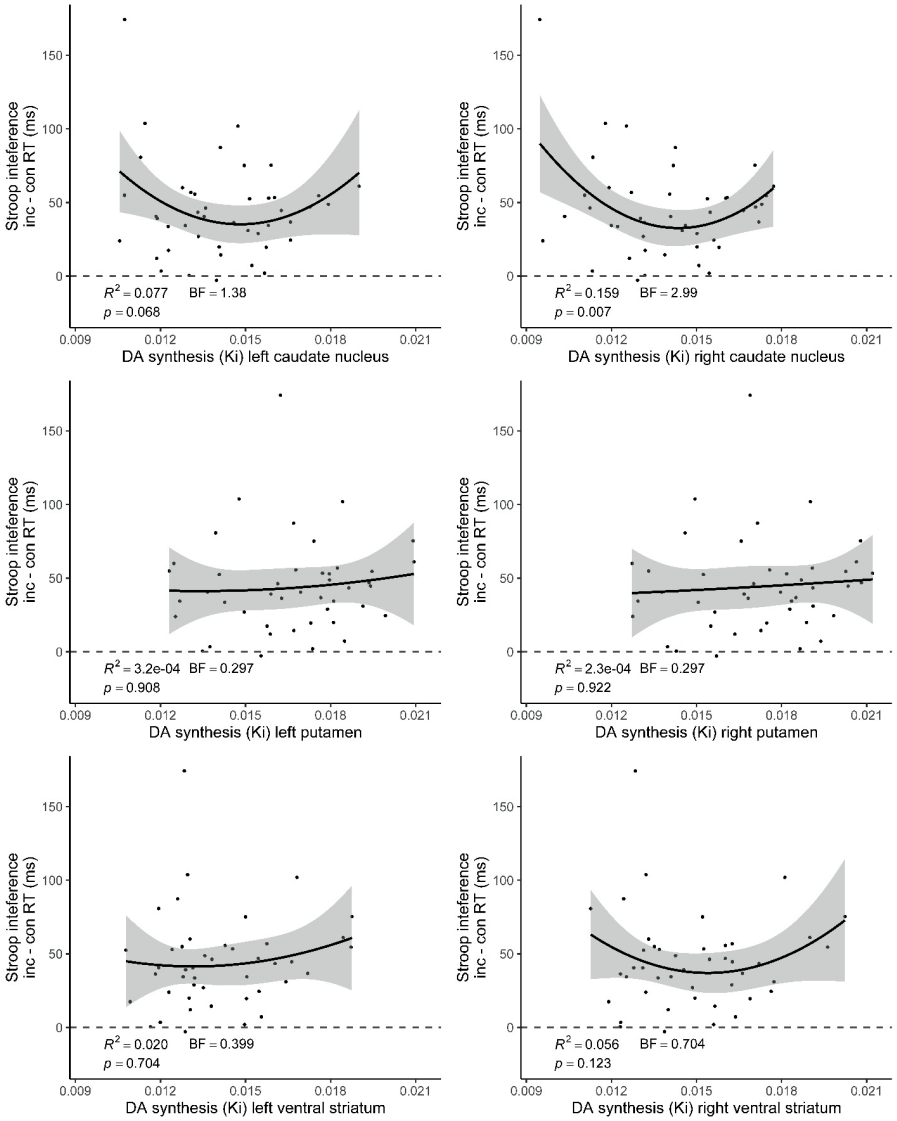

FIGURE S6.3 | Quadratic K_i-related effect on Stroop interference (mean RT incongruent trials minus mean RT congruent trials) in the six ROIs for uninformed low reward trials. Shaded area around the regression line represents 95% confidence interval. RT (ms) = response time in milliseconds; K_i = [^{18}F]DOPA uptake, reflecting dopamine synthesis capacity; N = 44. NB: Quadratic relationship between dopamine synthesis capacity in the right caudate nucleus and Stroop interference without the participants with the highest Stroop interference: R^2 = 0.03, p = 0.292, BF = 0.481.

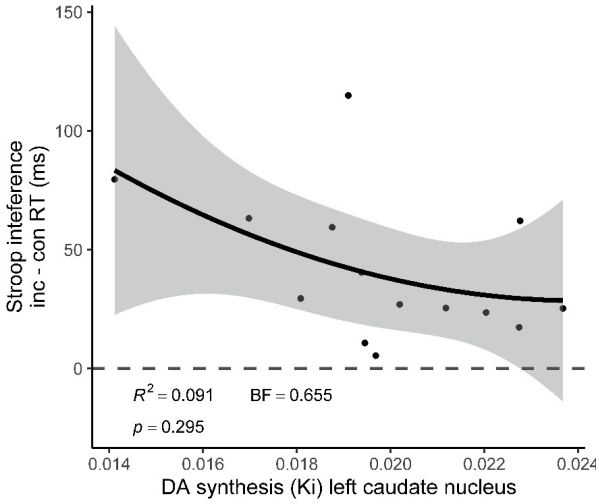

FIGURE S6.4 | Quadratic K_i-related effect on Stroop interference (mean RT incongruent trials minus mean RT congruent trials) in the left dorsal caudate nucleus for uninformed low reward trials in Aarts et al. Shaded area around the regression line represents 95% confidence interval. RT (ms) = response time in milliseconds; K_i = [^{18}F]DOPA uptake, reflecting dopamine synthesis capacity; *N* = 14.

Both in the current sample (Table S6.1) and the original sample (Table S6.2), baseline dopamine synthesis capacity was not associated with response times, neither in interaction with reward nor as main effect:

TABLE S6.1 | Effect of dopamine synthesis capacity and dopamine synthesis capacity x reward on response times in the current sample. Separate rmANOVA for each of the six regions of interest, including reward, congruency and information as within-subjects factors and dopamine synthesis capacity as covariate. *N* = 44.

	DAsynth		Reward x DAsynth	
	$F_{(1,42)}$	*p*	$F_{(1,42)}$	*p*
Left caudate nucleus	2.4	0.128	3.1	0.084
Right caudate nucleus[1]	7.5	0.009	3.8	0.058
Left putamen	0.0	0.833	1.1	0.299
Right putamen	0.1	0.804	1.3	0.268
Left ventral striatum	0.1	0.771	1.3	0.261
Right ventral striatum	0.3	0.596	2.9	0.095

[1]Corresponds to a negative correlation between dopamine synthesis capacity and response times. Effects when 1 participant with low dopamine synthesis capacity in the right caudate nucleus and an average RT of 4 standard deviations above the group mean was excluded: DAsynth: $F_{(1,41)}$ = 3.0, p = 0.092; reward x DAsynth: $F_{(1,41)}$ = 0.4, p = 0.535.

TABLE S6.2 | Effect of dopamine synthesis capacity and dopamine synthesis capacity x reward on response times in Aarts et al. Separate rmANOVA for each of the six regions of interest, including reward, congruency and information as within-subjects factors and dopamine synthesis capacity as covariate. *N* = 14.

	DAsynth		Reward x DAsynth	
	$F_{(1,12)}$	*p*	$F_{(1,12)}$	*p*
Left caudate nucleus	0.1	0.738	0.0	0.930
Right caudate nucleus	0.0	0.855	0.0	0.871
Left putamen	0.0	0.966	0.0	0.965
Right putamen	0.0	0.907	0.1	0.817
Left ventral striatum	0.2	0.702	0.0	0.893
Right ventral striatum	0.1	0.780	0.3	0.567

No evidence for a quadratic relationship between dopamine synthesis capacity and the effect of motivation on Stroop interference on uninformed trials

Although our hypothesis concerned a linear relationship between dopamine synthesis capacity and the effect of motivation on Stroop interference, a visual inspection of

Figure 6.2 led us to explore a quadratic relationship for the left and right caudate nucleus. To this end, we ran linear regressions (separately for both ROIs) in R using the lm function, including the quadratic z-scored K_i term as independent variable and the effect of motivation on Stroop interference in terms of RT on the uninformed trials as dependent variable. We applied a strict alpha level of 0.0036 (0.05÷14; 12 linear relationships and 2 additional quadratic relationships) to account for these additional analyses assessing the relationship between dopamine synthesis capacity and the effect of motivation on Stroop interference. We additionally ran the same Bayesian linear regressions in JASP to obtain a Bayes Factor for the effect.

However, there was no significant quadratic relationships between the effect of motivation on Stroop interference and dopamine synthesis capacity in the left (R^2 = 0.05, p = 0.144, BF = 0.719) or the right caudate nucleus (R^2 = 0.11, p = 0.028, BF = 2.271).

TABLE S6.3 | Interaction effects in terms of response times (RT) and error rates obtained from the rmANOVAs with dopamine synthesis capacity in each ROI as a single covariate. The dependent variable is Stroop interference (mean RT or error rate on incongruent trials minus mean RT or error rate on congruent trials). The sample is matched to the original sample from Aarts et al. in terms of age, resulting in N = 26.

	Reward x information x DAsynth			Reward x DAsynth		
	$F_{(1,24)}$	p	BF_{INC}	$F_{(1,24)}$	p	BF_{INC}
RT						
Left caudate nucleus	0.0	0.991	0.012	0.9	0.345	0.081
Right caudate nucleus	0.1	0.738	0.008	1.5	0.240	0.078
Left putamen	0.2	0.655	0.020	0.1	0.749	0.084
Right putamen	0.1	0.710	0.017	0.1	0.707	0.076
Left ventral striatum	0.0	0.931	0.015	0.1	0.737	0.070
Right ventral striatum	0.1	0.797	0.033	0.0	0.963	0.093
Error rate						
Left caudate nucleus	0.1	0.806	0.121	0.1	0.717	0.231
Right caudate nucleus	0.2	0.683	0.180	0.0	0.848	0.281
Left putamen	1.5	0.236	0.351	0.0	0.879	0.369
Right putamen	2.4	0.138	0.391	0.3	0.583	0.432
Left ventral striatum	0.7	0.397	0.138	0.0	0.933	0.238
Right ventral striatum	0.2	0.674	0.218	0.0	0.931	0.323

Note: p-values below a Bonferroni-corrected alpha-value of 0.0042 were considered significant.

TABLE S6.4 | Interaction effects in terms of response times (RT) and error rates obtained from the rmANOVAs with dopamine synthesis capacity in each ROI as a single covariate. The dependent variable is Stroop interference (mean RT or error rate on incongruent trials minus mean RT or error rate on congruent trials). The sample is matched to the original sample from Aarts et al. in terms of individual average RT across all trials, resulting in N = 29.

	Reward x information x DAsynth			Reward x DAsynth		
	$F_{(1,27)}$	p	BF_{INC}	$F_{(1,27)}$	p	BF_{INC}
RT						
Left caudate nucleus	0.5	0.465	0.094	1.2	0.282	0.099
Right caudate nucleus	0.1	0.780	0.009	2.5	0.125	0.098
Left putamen	2.2	0.153	0.005	0.0	0.938	0.037
Right putamen	2.2	0.147	0.005	0.0	0.932	0.037
Left ventral striatum	0.6	0.459	0.004	0.0	0.935	0.039
Right ventral striatum	0.2	0.636	0.004	0.1	0.730	0.048
Error rate						
Left caudate nucleus	0.2	0.651	0.016	0.0	0.884	0.041
Right caudate nucleus	0.0	0.884	0.014	0.0	0.945	0.054
Left putamen	2.8	0.106	0.028	0.2	0.697	0.082
Right putamen	5.6	0.025[1]	0.041	0.0	0.936	0.072
Left ventral striatum	0.4	0.551	0.013	0.5	0.490	0.073
Right ventral striatum	0.4	0.517	0.014	0.0	0.954	0.085

Note: p-values below a Bonferroni-corrected alpha-value of 0.0042 were considered significant.
[1]p-value does not survive correction for multiple comparisons. However, for clarity we report the interaction effect of reward x DAsynth in the right Putamen on Stroop interference (error rate): informed trials: r = -0.21, p = 0.266; uninformed trials: r = 0.29, p = 0.131.

TABLE S6.5 | Interaction effects obtained from multiple linear regression analyses assessing the effect of individual average RT across all trials on motivational effects on Stroop interference (incongruent trials minus congruent trials) in terms of response times (RT) and error rates. Separate analysis for each ROI.

	Reward x information x DAsynth		Reward x DAsynth		Reward x information x DAsynth x RT		Reward x DAsynth x RT	
	β	*p*	β	*p*	β	*p*	β	*p*
RT								
Left caudate nucleus	5.2e3	0.207	-7.3e3	0.260	-5.9e1	0.416	1.3e2	0.251
Right caudate nucleus	4.7e3	0.260	-6.3e3	0.330	-4.2e1	0.510	1.1e2	0.280
Left putamen	4.4e3	0.248	-7.0e3	0.249	1.8e1	0.870	1.3e1	0.939
Right putamen	4.5e3	0.219	-7.1e3	0.223	-2.7e1	0.797	8.8e1	0.602
Left ventral striatum	3.8e3	0.371	-6.5e3	0.334	-2.1e1	0.819	7.2e1	0.819
Right ventral striatum	3.1e3	0.424	-5.1e3	0.405	-5.1e1	0.486	1.1e2	0.333
Error rate								
Left caudate nucleus	3.0	0.878	2.5	0.934	1.1e-1	0.738	6.3e-2	0.906
Right caudate nucleus	-3.8	0.846	1.2e1	0.699	2.4e-1	0.419	-1.3e-1	0.780
Left putamen	-8.2	0.648	1.4e1	0.622	-2.2e-1	0.661	5.4e-1	0.501
Right putamen	-1.2e1	0.505	2.2e1	0.416	-1.8e-1	0.717	4.9e-1	0.535
Left ventral striatum	-3.8e-2	0.998	-2.1	0.947	1.0e-1	0.814	1.0e-1	0.881
Right ventral striatum	3.8	0.834	-5.6	0.847	2.1e-3	0.995	2.5e-1	0.650

Model: stroop_effect ~ DAsynth x reward x information x average RT

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CHAPTER 7

General discussion

To manage our goals, such as preparing soup, watching television and texting with a friend, we need cognitive control. In this thesis, I aimed to provide a deeper understanding of the cognitive and neural mechanisms that link cognitive control with motivation. Because when we focus on a task, specifically a cognitive task, it is not only about whether we are able to perform the task, but also about how motivated we are to perform well.

Here, I focused i) on the role of the neurotransmitter dopamine in making decisions about whether we want to perform a cognitive task (**chapter 2**), ii) on the effect of rewards on cognitive performance and decision-making about cognitive effort (**chapters 3-6**) iii) and on whether rewards affect cognitive stability versus flexibility (**chapters 3-5**). Across the experiments, I assessed whether the effects of dopaminergic medication or reward varied as a function of individual differences related to dopamine transmission, such as trait impulsivity (**chapter 5**) or dopamine synthesis capacity (**chapters 2 and 6**). Below, I will shortly summarize the main findings of the experiments and interpret them considering previous literature, while also discussing limitations. This will be followed by directions for future research.

The motivation-enhancing effect of methylphenidate is stronger in individuals with high striatal dopamine synthesis capacity

Chapter 2 examined whether the dopaminergic drug methylphenidate affected people's motivation for completing a cognitive working memory task versus leisure and whether the extent of this effect depended on baseline dopamine synthesis capacity, indexed by a PET scan using the radiotracer [^{18}F]DOPA. Methylphenidate increased participant's motivation for the cognitive task versus leisure and this effect was stronger for participants with higher baseline dopamine synthesis capacity. However, administration of the selective dopamine D2-receptor antagonist sulpiride, included in the design to test the dopamine-specificity of the effects of methylphenidate, showed no significant effects.

Interpretation and implications

These findings are in line with a role for dopaminergic medication in both cognitive control (Arnsten et al., 2015; Cools & D'Esposito, 2011; Goldman-Rakic, 1997) and decision-making (Chong et al., 2015; Le Bouc et al., 2016; Mcguigan et al., 2019; Salamone et al., 2009; Wardle et al., 2011). An important implication of these findings regarding the mechanisms of methylphenidate's effect on cognitive control, and

particularly cognitive improvement, is that it acts on our motivation for cognitive control, rather than or in addition to our cognitive abilities. This is consistent with previous theorizing stating that motivation plays a role in cognitive effort exertion and performance improvements (Kurzban et al., 2013) and that increases in dopamine transmission enhance the weight on the benefits versus the costs, resulting in higher motivation for cognitive control (Collins & Frank, 2014; Cools, 2016; Shenhav et al., 2013, 2017; Westbrook et al., 2020). Together with the findings reported in a parallel experiment, part of the same overarching study, showing that methylphenidate increased motivation for a high demanding cognitive task over a low demanding cognitive task (Westbrook et al., 2020), these data strengthen the link between striatal dopamine and cognitive motivation (Aarts et al., 2011; Mcguigan et al., 2019). This also has important clinical implications. Methylphenidate administration is often associated with improved attention in individuals with attention deficit hyperactivity disorder (ADHD) (Volkow et al., 2012). This has been argued to involve striatal motivational circuits (Sergeant, 2000, 2005; Volkow et al., 2011, 2012). The current finding that methylphenidate increased cognitive motivation across the group might imply that the effect of methylphenidate on attention in ADHD patients is indeed, at least partly, due to motivational effects.

The observation that the effect depended on higher dopamine synthesis capacity in the nucleus accumbens is consistent with earlier reports in which the effect of dopaminergic medication on cognitive control or cognitive demand avoidance depended on individual difference in baseline measures, such as impulsivity and working memory capacity (Clatworthy et al., 2009; Cocker et al., 2012; Cools et al., 2007; Froböse et al., 2018; Kimberg et al., 1997; Kimberg & D'Esposito, 2003; Mehta et al., 2000).

An open question is why methylphenidate exhibited its strongest effect in high-dopamine compared with low-dopamine individuals. A question that is particularly pertinent given opposing results in the parallel study by Westbrook et al., showing that methylphenidate increased motivation for a high demanding cognitive task over a low demanding cognitive task, particularly in *low dopamine* individuals (Westbrook et al., 2020). While the study by Westbrook et al. examined choices between clearly defined costs and benefits, the study reported in **chapter 2** examined decision-making with an emphasis on opportunity costs, which were not explicitly defined. Therefore, one possible explanation for these apparently conflicting results is the pivotal role of opportunity costs in the task applied in the study described in **chapter 2**, but not in the task of Westbrook et al. In this latter study, computational models indicated that methylphenidate increased motivation by biasing sensitivity to the benefits (monetary payoff) versus the costs (cognitive demand) of the cognitive task (Collins & Frank, 2014;

Westbrook et al., 2020). Moreover, a higher preference for the high-demanding option at baseline, particularly in high-dopamine participants, might have reduced the range for further increases in the weight on the benefits in those participants. Conversely, in **chapter 2** I show that methylphenidate does not interact with the benefits of the task. Therefore, it is possible that methylphenidate acted by reducing the cost, particularly the opportunity cost of performing the cognitive task (when one would choose to perform the task, they would forego the option to enjoy leisure time). Participants indeed exhibit a strong aversion to the task, possibly reflecting strong opportunity costs. On placebo, individuals with high dopamine synthesis capacity in the nucleus accumbens, an area arguably associated with signaling opportunity costs (Niv et al., 2007), showed a lower willingness to perform the task. This lower willingness might have generated an increased dynamic range for methylphenidate to reduce feelings of opportunity cost, thereby increasing cognitive motivation (Figure 7.1A). These contrasting effects of methylphenidate on benefits versus costs are concurrent with the neurobiological architecture of dopamine's contrasting effects on the direct Go pathway and indirect NoGo pathway in the basal ganglia. Dopamine facilitates activation of the Go pathway, associated with the benefits of an action, whereas it inhibits activation of the NoGo pathway, associated with the costs of an action (Collins & Frank, 2014).

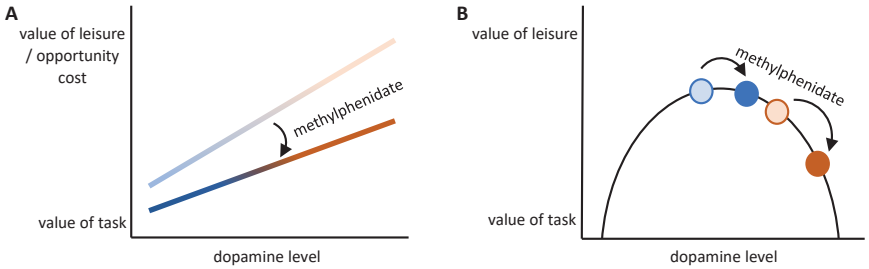

FIGURE 7.1 | Possible explanations for the effect of methylphenidate being strongest in individuals with high baseline dopamine synthesis capacity. **A** – On placebo, individuals with high dopamine synthesis capacity showed a lower subjective value of the cognitive task, potentially due to a higher experience of opportunity cost. This might have generated an increased dynamic range for methylphenidate to reduce feelings of opportunity cost by a certain factor, thereby increasing the value of the task more in high-dopamine individuals. **B** - An alternative explanation is that methylphenidate acted by shifting the value of leisure from suboptimal to optimal in low-dopamine individuals, while eliciting a shift from optimal to supra-optimal in high-dopamine individuals, thereby paradoxically lowering the value of leisure and increasing the value of the cognitive task.

An alternative explanation is that methylphenidate acted by increasing the value of leisure, rather than decreasing the opportunity cost of the task, consistent with dopamine's role in value-signaling (Collins & Frank, 2014; Hamid et al., 2016; Wardle et al., 2011). Methylphenidate might have shifted this value of rest from suboptimal

to optimal in low-dopamine individuals, while eliciting a shift from optimal to supra-optimal in high-dopamine individuals, thereby paradoxically lowering the value of rest and thus increasing cognitive motivation (Figure 7.1B).

Thus, I speculate that a differential emphasis on the benefits versus the costs of the task might have rendered different results in the two experiments.

Limitations

The study described in **chapter 2** provides valuable insights into the mechanisms of cognitive motivation but is not without limitations.

First, I cannot exclude the possibility that the effect of methylphenidate reflected changes in noradrenaline, rather than dopamine transmission, as the drug blocks the reuptake of both neurotransmitters. Moreover, sulpiride, which selectively alters dopamine transmission, yielded no significant effects. However, as already discussed in **chapter 2**, it is possible that the dosage of sulpiride was suboptimal. Together with the effect being predicted by dopamine synthesis capacity, I consider it more likely that the effect reflected dopaminergic transmission, although I would refrain from drawing firm conclusions.

Second, I derive conclusions about dopamine synthesis-related effects in the striatum. However, I cannot address a potential parallel locus of action in the prefrontal cortex, as the uptake signal of our radiotracer in the prefrontal cortex is too low. Future studies should employ combined PET-fMRI designs to unravel potential prefrontal dopamine-dependent effects of methylphenidate on cognitive motivation.

Third, conclusions are based on an index of dopamine synthesis capacity. While this is considered to contribute to the level of dopamine transmission (Egerton et al., 2010), it is an indirect measure. Other factors, such as transporter density, dopamine receptor availability and dopamine release should also be considered to provide a more complete picture of the baseline-dependency of methylphenidate's mechanisms of action.

Fourth, as already eluded to above and in **chapter 2**, the study was designed to place more emphasis on opportunity costs. However, opportunity costs were not manipulated directly, which prevents me from drawing firm conclusions about the effect of methylphenidate on opportunity costs. Therefore, future studies could shed light on these mechanisms by more systematically manipulating the value of the alternative, leisure option (see also the Future Outlook section below).

Fifth, I want to highlight the fact that our study sample consisted of healthy participants. It is unclear what the effects of methylphenidate on cognitive motivation are in patients with for example Parkinson's disease or ADHD. Apathy, characterized by a general lack of interest and diminished motivation, is a common behavioral symptom in patients with Parkinson's disease, a disorder characterized by reduced dopamine transmission in the striatum. Although more studies are needed, methylphenidate potentially reduces apathy in patients with Parkinson's disease (Chong & Husain, 2016; Devos et al., 2013), in line with the positive effects of methylphenidate on motivation reported in **chapter 2**. There is no strong evidence for a relationship between ADHD and dopamine synthesis capacity. Research in other populations with impulsive behavior, such as pathological gamblers, have been associated with high levels of striatal dopamine synthesis capacity (van Holst et al., 2018). The present results suggest that in situations in which opportunity costs are highly pronounced, methylphenidate particularly increases cognitive motivation in those populations. However, the relative lack of evidence for a relationship between ADHD and dopamine synthesis capacity might be suggestive of large heterogeneity in this population. An important question is therefore whether dopamine synthesis capacity would be a better predictor of the effect of methylphenidate than the diagnosis ADHD.

Lastly, I was interested in exploring dopamine drug effects on choices between cognitive stability versus flexibility. Inspired by literature regarding the dynamics between cognitive stability and flexibility (Cools & D'Esposito, 2011; Fallon et al., 2017; Musslick et al., 2018), I expected that increases in striatal dopamine would result in a shift toward more motivation for cognitive flexibility at the expense of stability. However, the data showed no strong evidence for methylphenidate or sulpiride shifting this balance. Contrary to earlier studies, in which participants preferred a similar flexible update task over a stable ignore task (Froböse et al., 2018; Papadopetraki et al., 2019), there was no difference between the value of the two tasks under placebo, which might explain the lack of drug effects. Therefore, in the subsequent chapters, I aimed to develop a paradigm that we would use for future testing of dopamine's effects on the motivational modulation of the stability/flexibility balance. As will become clear, however, these novel paradigms also did not generate unequivocal results.

The effects of rewards on cognitive control are small and variable

In **chapters 3-5** I focused on developing a paradigm with the goal to assess the role of dopamine in the *incentivization* of stable versus flexible cognitive control, rather than the *valuation* of different cognitive tasks.

Chapter 3 assessed whether contextual aspects modulate incentive effects on the stability/flexibility balance. Specifically, I tested whether incentive motivation potentiated strategic meta-control using the same working memory paradigm as in chapter 2, that distinguishes between two different trial-types, one requiring cognitive stability and the other requiring flexibility. I manipulated the extent to which participants could exert strategic meta-control by varying the frequency of one trial-type over the other, allowing participants to prepare for the high-frequent trial type. I expected participants to perform better on the high-frequent trial-type, and that greater incentive motivation would strengthen this effect. However, the results did not provide conclusive evidence for this hypothesis. Planned analyses did not demonstrate effects of incentive motivation on strategic meta-control in terms of accuracy. There were also no main effects of incentive motivation or the frequency manipulation. Exploratory reaction time analyses showed greater motivation-related slowing on flexible update trials when this was the high-frequent trial-type. However, we did find a performance improvement, for both stability and flexibility trial-types, when the majority of the trials was of the stability type. Thus, a high proportion of stability-requiring trials might have had a general positive effect on working memory by increasing task engagement, cognitive maintenance, or attention to the experiment. Importantly though, this effect was not modulated by incentive motivation.

The lack of incentive motivation effects in **chapter 3** does not mean that there would be no effects of different reward manipulations. In **chapter 4**, I therefore looked at effects of reward that are independent of performance, rather than effects of incentive motivation, where rewards are performance contingent. In line with prior work showing that reward promotes task-switching (via its action on the striatum) (Aarts et al., 2011), **Chapter 4** examined whether highly rewarding environments are also associated with improved cognitive flexibility versus cognitive stability in the context of working memory. Furthermore, inspired by studies on foraging behavior suggesting that highly rewarding environments that carry high opportunity costs promote flexible exploration (Charnov, 1976; Constantino & Daw, 2015; Kolling et al., 2012; Le Heron et al., 2020), I hypothesized that highly rewarding environments would also reduce the subjective cost of cognitive flexibility versus stability, measured with a subsequent cognitive effort discounting procedure. However, I did not find evidence that the reward environment affected the balance between cognitive stability and flexibility, nor did I find any general effects of reward environment.

Because **chapters 3 and 4** did not yield significant results, I wondered whether any effects of reward on cognitive performance and the stability/flexibility balance could be recovered when looking at individual differences in **Chapter 5**. I tested whether reward motivation enhanced performance on tasks requiring cognitive flexibility

at the expense of performance on tasks requiring cognitive stability, using the same working memory paradigm as in the previous chapters. I measured trait impulsivity, a putative proxy of dopamine transmission, to capture potential individual variability in the effects of reward motivation. Planned analyses of accuracy revealed no significant effects. Exploratory analyses on reaction times revealed that participants responded more slowly on high versus low reward trials. However, this slowing was selectively reduced on trials requiring flexibility, but not on trials requiring stability, and only in high-impulsive individuals. Put forward with caution, this could be suggestive of increased cognitive flexibility versus stability. However, as will be further explained in the Limitations below, it is unclear how response times should be interpreted.

The lack of reward effects on accuracy in the experiments described in the previous chapters might suggest that the current paradigm is not sensitive enough to reward manipulations. In **chapter 6**, I therefore employed an established paradigm, a Stroop task which has been shown to be sensitive to reward manipulations, to look at the effect of reward motivation. Moreover, I also measured dopamine transmission more directly by looking at striatal dopamine synthesis capacity. I aimed to replicate a previous finding that reward improved Stroop control in low-dopamine individuals, while impairing it in high-dopamine individuals (Aarts et al., 2014). I re-invited the participants from **chapter 2**, whose dopamine synthesis capacity was already indexed using an [^{18}F]DOPA-PET scan, to perform the exact same Stroop task, measuring the effect of reward motivation on interference control. However, the effect of reward motivation did not correlate with striatal dopamine synthesis capacity. I also did not find any main effects of reward motivation, independent of dopamine synthesis capacity. It is possible that the discrepancy between the findings of the two studies reflects the use of the potentially less sensitive [^{18}F]DOPA radiotracer to index dopamine synthesis capacity in the current study, versus [^{18}F]FMT in the study by Aarts et al., as is more thoroughly discussed in **chapter 6** and in the Limitations section below.

Interpretation and implications

After having assessed the effect of methylphenidate on *whether or not* participants wanted to perform a cognitive task in **chapter 2**, the studies reported in **chapters 3-6** examined the *intensity* of cognitive control as a function of motivational cues and contexts (Norman & Shallice, 1986; Shenhav et al., 2013, 2017). The ultimate aim of these experiments was to develop a paradigm to test the effect of dopaminergic drugs on the link between incentive motivation and the cognitive stability/flexibility balance. Yet, since I did not succeed to establish a paradigm that was sensitive to manipulations of incentive motivation, this goal was not further pursued.

Reward motivation, also called incentive motivation, refers to the motivating or invigorating effect of a prospective reward. Reward motivation has often been demonstrated to enhance cognitive control, both in terms of better accuracy and faster responding on cognitive tasks (Padmala & Pessoa, 2011; Pessoa & Engelmann, 2010; Yee et al., 2016). Several studies have attributed this effect to reward motivation recruiting the frontoparietal control network to "sharpen" task-relevant information in a preparatory manner (Braver, 2012; Chiew & Braver, 2016; Etzel et al., 2016; Hall-McMaster et al., 2019; Parro et al., 2018). Our results in **chapter 3** differed from these earlier studies, showing no effect of reward motivation on such preparatory meta-control or cognitive performance across the task. As discussed in the limitations section below, and in more detail in **chapter 3**, the incentive structure of the paradigm might have limited the advantage of engaging additional control to improve performance, rendering the paradigm less sensitive to reward manipulations.

I therefore turned to different reward structures in **chapters 4 and 5**. Moreover, because of the association between reward and dopamine (Schultz, 1997), I hypothesized that reward would affect cognitive control in a task-selective manner. This was motivated by prior evidence indicating that dopamine impacts cognitive flexibility or stability depending on whether it acts on the striatum or prefrontal cortex respectively (Cools & D'Esposito, 2011; Cools & Robbins, 2004; Crofts et al., 2001). Thus, depending on whether reward primarily acts on the striatum or the prefrontal cortex, reward was predicted to improve cognitive flexibility or stability, respectively (Aarts et al., 2011).

In **chapter 4**, I examined the effect of non-contingent reward environments on cognitive stability versus flexibility in terms of both performance and perceived effort costs. In **chapter 5** I tested the effect of performance-contingent rewards, or incentive motivation, on the stability/flexibility balance. The lack of effects in these studies is at odds with earlier reports, showing differential reward-effects on stability and flexibility (Braem et al., 2013; Dreisbach & Fröber, 2019; Fröber et al., 2019). Importantly though, in Bream et al. (2013), participants performed a task-switching paradigm in which a randomly chosen positive or negative picture was presented after each correct trial. The valence of the preceding picture was used to determine differences between positive and negative affect on switch-costs. In other words, they tested the effect of a previously received reward on performance, rather than the effect of incentive motivation. Moreover, when a participant was correct, there was still a chance that a negative picture would be presented on screen. Conversely, the study in **chapter 5** examined the effect of (positive) incentive motivation on performance, a difference in design that could possibly account for the discrepant results. A recent study investigated the effect of *increases* in incentive motivation, rather than high or low incentives (Fröber et al., 2019). They found that increases in incentive, but not

incentives that remained high, increased flexible behavior, such that participants chose to perform task-switches rather than task-repeats. This might indicate that sequential effects of rewards or incentives are more important for behavior than only the current reward value, a topic I will return to in the Future Outlook session below.

Prior work has suggested that individual variation in the effects of reward motivation on cognitive control depends on dopamine transmission or dopamine-related personality traits (Aarts et al., 2010, 2012, 2014; Chib et al., 2012; Mobbs et al., 2009; van Holstein et al., 2011). However, I also did not find robust reward effects when taking into account trait impulsivity in **chapter 5**. Because thus far I had only used the color wheel working memory task, I then decided to employ an established paradigm, a word-arrow Stroop task previously demonstrated to be sensitive to reward manipulations, to assess effects of reward motivation in **chapter 6**. Even though Aarts et al. (2014) had previously reported effects of reward motivation as a function of striatal dopamine synthesis capacity in 14 individuals, using the same paradigm, I was not able to replicate these results in a larger sample of 44 individuals.

While it might be possible that effects could have been detected at the neural but not the behavioral level (Fallon & Cools, 2014; Krawczyk et al., 2007; Soutschek et al., 2015) and I did observe exploratory effects, albeit small and ambiguous, on response times, it is remarkable that I did not detect any robust effects of reward on cognitive meta-control (**chapter 3**), the flexibility-stability balance (**chapters 3, 4 and 5**), or as a function of individual differences (**chapters 5 and 6**). Even more surprising is that I also did not find any main effects of our reward manipulations. As will be laid out in the limitations section below, there were some weaknesses in our behavioral designs that should be improved before drawing firm conclusions, but the lack of robust effects across the four studies suggests that the effects of reward on cognitive control might not be as strong as previously believed.

What does this tell us about the origin of the costs of cognitive effort, as required for working memory and other cognitive control tasks? Longstanding metabolic ego-depletion accounts of cognitive control costs (Baumeister et al., 1998), which state that engaging in effortful tasks depletes our mental resources, leading to lower performance on subsequent tasks (much like when our muscles become fatigued after physical effort exertion), have been criticized based on the observation that control costs can be reduced by incentive motivation (Botvinick et al., 2009; Botvinick & Braver, 2015; Braver et al., 2014; Kurzban et al., 2013). Does the present lack of motivational effect on cognitive control question these motivational accounts in the context of this task?

One possible explanation might be that incentive motivation, or pharmacological manipulations, only affect cognitive performance itself when someone is not already maximally motivated or invested in a task. Once someone is already intrinsically motivated or invested by, for example, a prior deliberate choice to perform the task, incentive motivation or pharmacological manipulations will not have a strong additional effect on performance anymore. In line with this argument are the findings in a study already mentioned above, where they did not observe reliable effects of incentive (either high versus low or remain high versus increasing) on switch versus repeat *performance*, only on *choices* for task-switches (Fröber et al., 2019). Similarly, methylphenidate was shown to affect choices about whether to perform a high or low cognitive demand task (as a function of trait impulsivity), but this was not paralleled by effects on performance after participants had made their choice (Froböse et al., 2018). Of note here is that participants informally reported to enjoy playing the color wheel working memory task in **chapters 3-5**, where a rewarded paradigm was used, whereas they reported feelings of boredom in the unrewarded paradigm in **chapter 2**, indicative of the introduction of rewards having a general energizing or motivational effect on the participants. Participants might thus have been intrinsically motivated by the rewarded task, so that the reward cues did not have an additional effect anymore on the trial-level.

Related to this theorizing is the notion of a failure-to-engage (De Jong, 2000). De Jong states that, given there is time to prepare, participants only succeed on a portion of the trials in a cognitive task, as evidenced by markedly shorter response times than when there is little time to prepare. On the other trials, participants fail to engage, or fail to prepare for an upcoming trial, with relatively long response times as a result. This would suggest that on trials with short response times, participants perform at their ceiling level, whereas they could in principle still improve on trials with longer response times. Thus, any effects of motivation would be primarily be recoverable on those trials with longer response times (De Jong, 2000; Nieuwenhuis & Monsel, 2002). However, an analysis of those trials in the study reported in **chapter 3** did not yield any effects of incentive motivation. Although there was less opportunity for participants to prepare for the task in the subsequent studies, it would be interesting to see if any motivational effects can be recovered in these later studies that use different reward manipulations and take into account individual differences in baseline measures.

Limitations

As discussed in the respective chapters, various features of the behavioral paradigms used in **chapters 3 to 5** might be optimized and warrant caution. First, participants' goal in **chapter 3** was to maximize bonus points, which could be received by performing

above a certain threshold. This threshold was very lenient, supported by a very high percentage of trials on which participants obtained bonus points. This might have limited the degree to which extra cognitive effort expenditure could increase their bonus points. **Chapter 5** employed a more stringent threshold, which however also did not result in a successful reward manipulation. Another possibility for potential future work on this paradigm is to linearly decrease the points that are obtained as accuracy declines.

Second, I primarily assessed reward effects by looking at working memory performance. Perhaps it is something about this paradigm in particular that makes it insensitive to reward manipulations. For example, the multiple consecutive phases which rapidly follow each other or the fact that the cues as to whether to ignore or update appear on the screen at the same time as the intervening stimuli. These aspects could have made it hard for participants to exert additional control in response to reward cues. However, in **chapter 3** we also did not find effects of reward on performance, despite the fact that this study allowed for preparatory control. Thus, although it is unclear why our paradigm seems insensitive to reward manipulations, using other cognitive paradigms, such as attentional or task switching paradigms, might well have produced different results.

Contrary to measures of accuracy, the color wheel task did seem to be sensitive to reward manipulations in terms of response times (**chapters 3 and 5**). The question is why we did observe effects on response times. It is possible that we found effects in **chapter 3** because fast responding was emphasized. As soon as they had decided on the color, participants had to move their mouse as fast as possible to give a response. However, this cannot explain the effect in **chapter 5**, where they had ample of time to respond. Moreover, a limitation is that response times are difficult to interpret, as slower response times can indicate either a deliberate increase in caution, with the goal to improve accuracy, or poorer performance. Future studies could employ response time distributions, such as drift diffusion models, which simultaneously estimate decision thresholds, i.e. the amount of information one wants to collect before reaching a decision, and drift rates, i.e. the rate at which information is collected. This could shed more light on whether slow response times imply more caution (higher decision thresholds) or poorer performance (slower information collection).

Moreover, the reward-related effect on response times we found in **chapter 5** was only isolated when taking into account trait impulsivity measured using the self-report Impulsive Behavior Scale (UPPS), not another widely used self-report questionnaire of trait impulsivity, the Barratt Impulsiveness Scale (BIS-11), limiting conclusions that can be drawn from this finding.

It is possible that the discrepancy between the findings by Aarts et al. (2014) and the study reported in **chapter 6** reflects the use of the potentially less sensitive [^{18}F]DOPA radiotracer to index dopamine synthesis capacity in the current study, versus [^{18}F]FMT in the study by Aarts et al. [^{18}F]DOPA, but not [^{18}F]FMT, can be metabolized in the periphery. Metabolites can then cross the blood-brain-barrier and distribute evenly throughout the brain, lowering the signal-to-noise ratio. Moreover, [^{18}F]DOPA metabolites have a higher affinity for the vesicular monoamine transporter compared with [^{18}F]FMT metabolites, leading to increased cell clearance of radiolabeled [^{18}F]DOPA metabolites when scanning for extended periods of time, further reducing signal. Although entacapone was administered before PET scanning to inhibit peripheral metabolism of [^{18}F]DOPA and cell clearance should be limited in the scanning period that was used in our study (the first 90 minutes after tracer injection), it is possible that another measure of dopamine synthesis capacity, such as [^{18}F]FMT, would have given different results.

Future outlook

As is inherent to scientific research, several new questions arise based on the findings presented here.

Does methylphenidate affect performance via its effect on motivation?

Prior research already established that methylphenidate can modulate cognitive performance. Here, we have seen that this effect might at least partly be due to methylphenidate modulating the motivation for cognitive control. An important question is whether this modulation of motivation also results in a modulation of performance. An additional question is how this works at the neural level. Future work, using fMRI and dynamic causal modeling or connectivity analyses, could disentangle whether methylphenidate modulates cognitive motivation by affecting striatal activation, and whether this affects striatal output to the prefrontal cortex, thereby altering performance on the behavioral level. Alternatively, methylphenidate might directly act on both the striatum and prefrontal cortex. It might alter the signal-to-noise ratio of cognitive representations by acting on the prefrontal cortex, and merely modulate the strengths of these representations by its effect on the striatum and striatal output to the prefrontal cortex.

How to predict the level of dopamine synthesis capacity?

I have established that the effect of methylphenidate depended on dopamine synthesis capacity, as indexed using a PET scan. This finding is promising for future (clinical)

pharmacological studies and further experimental research aiming at isolating effects of drugs like methylphenidate. However, PET scans are expensive and highly invasive, as it requires a radiolabeled isotope to be injected into the body. Is there a way to predict dopamine synthesis capacity based on different measures, such as self-report measures, working memory capacity or eye-blink rate? The study reported in **chapter 2** is part of a larger overarching study, in which a number of putative proxy variables were also collected, including eye-blink rate and working memory capacity measure. One goal of this study is indeed to develop a model that can predict striatal dopamine synthesis capacity, using a combination of self-report, cognitive and physiological measures. Such a proxy model could serve to facilitate decisions about the prescription and use of drugs of which the effects depend on dopamine synthesis capacity.

What is the role of opportunity costs in deciding whether to exert cognitive control?

In **chapter 2**, I speculate that methylphenidate exerted its effect on cognitive motivation via a modulation of opportunity costs. Opportunity costs were emphasized by letting the participant choose between performing a cognitive task and leisure, rather than a different task. Yet, I did not manipulate or control opportunity costs directly. Future studies could more directly test the effect of opportunity costs on decisions about whether to exert cognitive control and whether dopaminergic medication modulates these effects. For example, by manipulating the value of an alternative activity, such as a video game in which participants can win a certain number of points. Similar to **chapter 1**, participants would make decisions about whether they want to perform the cognitive task for more money or play the game for less money. Another option is more akin to a patch-leaving task, in which participants have a certain period to perform a cognitive task, gaining points for each completed trial. They can quit the task any time they like to play another game, of which the value is parametrically modulated but less than that of the cognitive task, for the remainder of the time period. The number of trials they complete before they quit the cognitive task can be taken as an index of their cognitive motivation.

What are the effects of sequential reward manipulations on cognitive stability versus flexibility?

The findings reported in this thesis suggest that the effect of reward motivation manipulations on cognitive control are not very robust. Does this mean that cognitive control is not affected by motivation? This thesis does not provide a definitive answer to this question, but paves the way to investigate different reward manipulations. Future studies could dive into sequential effects of rewards. For example, it has been

reported that reward improved the extent to which participants flexibly prepared for an upcoming cognitive task, but only when a high reward followed a low reward, not when rewards were continuously high (Shen & Chun, 2011). Other sequential reward effects on cognitive control have been found when manipulating the average reward rate. A period in which participants received more reward on average resulted in better cognitive (Otto & Daw, 2019) and motor performance (Beierholm et al., 2013; Guitart-Masip et al., 2011) compared with a period in which participants received less reward on average. Relevant here is that the immediate reward, the reward that was associated with the current trial, did not affect performance. It would be interesting to test whether such sequential reward effects differ for tasks requiring cognitive stability or cognitive flexibility.

Cross-species research

Another opportunity is to complement human research with animal research. Even though not all results obtained using animal research can be directly translated to human research, animal research nonetheless provides us with tools that are not possible, or ethically responsible, to use in human research. For example, to test dopamine's role in cognitive motivation or the balance between stability and flexibility, different doses of dopaminergic drugs can be locally injected in areas of the striatum or prefrontal cortex to examine effects on choice and performance, for example using a task-switching paradigm, in which rodents (choose to) perform task-repeats or task-switches. Moreover, neurotransmitter release or the activity of neurons can be monitored using microdialysis or voltammetry, and phasic dopamine or noradrenaline transmission can be manipulated using optogenetic manipulations. This way, more precise conclusions about the link between dopamine (or other neurotransmitters), motivation and cognitive control in behaving animals can be drawn.

Concluding remarks

Cognitive control is an important hallmark throughout our daily lives. We need it to pursue our goals, to attend to a goal while suppressing irrelevant information and to flexibly switch between goals when needed. In this thesis, I have addressed the role of motivation in cognitive control, and how we can modulate this motivation. Specifically, I have assessed pharmacological approaches to modulate decision-making about whether to exert cognitive control, and I have manipulated reward motivation to affect cognitive control. Here, I demonstrated that methylphenidate increases motivation for cognitive control and that the extent of this effect depends on striatal dopamine synthesis capacity. I have also shown evidence that suggests that the effects of reward

on cognitive control are not as strong or straightforward as previously thought, which might have important implications for education or the workplace. The studies in this thesis show the importance of employing various behavioral paradigms to test cognitive theories, thereby also showing the importance of replication studies. As always, these studies have generated many more questions to the neurocognitive puzzle.

An anecdote about trait impulsivity, expectations and false positives

Doing research is not always (or almost never) a smooth process. The following example illustrates what the process might look like in practice, and what we can learn from it.

When analyzing the data for chapter 2, we wanted to explore whether the effect of methylphenidate depended on trait impulsivity. This was inspired by prior evidence demonstrating that trait impulsivity is related to dopamine transmission (Buckholtz et al, 2010; Lee et al, 2009; Kim et al, 2014; Reeves et al, 2012) and earlier work from our lab, showing that the effect of methylphenidate on cognitive effort avoidance depended on trait impulsivity (Froböse et al., 2018). Given the correlation between the effect of methylphenidate on cognitive motivation and dopamine synthesis capacity that we had already found, we were not surprised when we indeed found a very strong correlation between the effect of methylphenidate and trait impulsivity. Methylphenidate had a stronger positive effect on cognitive motivation in more impulsive individuals. An earlier version of chapter 2 included an additional paragraph about this explorative finding.

Only later, when we wanted to compare our demographic data, including trait impulsivity scores, with those in the study by Aarts et al. (2014) (chapter 6), we realized that the impulsivity scores of our study sample were particularly high. Too high. We assumed that our scores were calculated correctly, as they were independently scored and verified by two researchers. We therefore dug deeper into the raw material, particularly the questions that were included in the questionnaire that we had used. One question stood out, as it was seemingly unrelated, or at least less related to impulsive behavior ("I have regular medical/ dental checkups"). After checking various sources, we discovered that this question was indeed not part of the official questionnaire. Even worse, we found out that we had used a different, earlier version of the questionnaire, which had never been validated. Some questions in this earlier version were the same as

those in the official version, others were left out or replaced, and some phrasings were reversed. Most importantly, the order of the questions was different in both versions. Because we had used the scoring sheet belonging to the official version to score the earlier version, our resulting scores were completely random and unrelated to trait impulsivity. This meant that the strong correlation we had found represented pure noise. Because the manuscript reporting this study was already under review, we had to contact the journal to halt the reviewing process. We then needed to recalculate the scores based on the correct scoring sheet and rewrite the manuscript. Of note here is that, based on those meaningful scores, there was no correlation with the effect of methylphenidate.

Of course, we all know that when we find a significant result, even when it is very strong, this could potentially be due to chance. After all, our inferences are often based on statistics. However, it is still important to realize and to be reminded of. The correlation we had found was strong and was expected based on previous literature, but it was still a false positive. Fortunately, we found out about it before the paper was accepted, but all the hassle that followed definitely reminded me to be cautious and to always bear in mind that a finding can be a false positive.

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Appendix

Nederlandse samenvatting

Het is een donderdagavond en ik ben soep aan het klaarmaken voor morgen. Wanneer de soep wat begint te sudderen ga ik op de bank zitten om mijn favoriete tv-programma te kijken. Alles wat er gebeurt met de deelnemers zal morgen uitvoerig worden besproken tijdens de lunchpauze. Dan krijg ik een berichtje van een vriendin. Na een aantal berichtjes heen en weer vertelt ze me over haar week. Ik wissel mijn aandacht af tussen het tv-programma en het verhaal van mijn vriendin. Plots wordt het verhaal erg interessant. Ik richt me nu volledig op het verhaal en vergeet het tv-programma. Midden tijdens het lezen van een van de berichten ruik ik ineens een brandgeur en ik ren snel naar het fornuis om mijn soep te redden.

Prestatie: kunnen of willen?

Het omgaan met verschillende doelen of taken, zoals het klaarmaken van soep, tv kijken en berichten lezen en versturen, is belangrijk in ons alledaagse leven. Soms moeten we ons focussen op een bepaalde taak, terwijl we het volgende moment weer van taak moeten wisselen omdat iets anders plots belangrijker is. Dit lukt ons soms beter dan op andere momenten en soms beter bij het doen van de ene taak dan de andere taak. Vaak denken we dat hoe goed we zijn in het uitvoeren van een taak vooral een afspiegeling is van hoe goed we iets *kunnen*. Het is echter ook heel belangrijk hoe graag we iets goed willen uitvoeren. Oftewel, hoe gemotiveerd zijn we? Het zal bijvoorbeeld niet als een verrassing komen dat mensen vaak beter presteren op een taak wanneer ze ervoor beloond worden. Bovendien zullen ze waarschijnlijk meer geneigd zijn een moeilijke of zware taak te verkiezen boven een simpele taak, als ze er maar genoeg beloning voor krijgen. Denk maar eens aan die keren dat je een snoepje mocht eten zodra je je kamer netjes had opgeruimd. Het lijkt er dus op dat onze prestatie op taken niet alleen een kwestie is van hoe goed we ergens in zijn, maar ook een afweging van of het de moeite wel waard is: Zijn de totale beloningen hoger dan de totale kosten?

Hoe deze relatie tussen prestatie en motivatie in elkaar zit is echter nog niet geheel duidelijk. Bijvoorbeeld, alhoewel mensen meestal beter worden op een taak wanneer ze hoger beloond worden, is dit niet altijd het geval en gaan sommige mensen hierdoor juist slechter presteren. Bovendien hebben eerdere onderzoeken uitgewezen dat beloning ervoor kan zorgen dat je beter wordt op bepaalde taken, maar slechter op andere taken.

Doel van het proefschrift

Het doel van dit proefschrift was om meer duidelijkheid te scheppen over deze relatie tussen motivatie en prestatie. Ik heb me hierbij specifiek gericht op cognitieve taken. Ik heb dit benaderd vanuit twee perspectieven: 1) Zien we effecten op cognitieve *prestatie* wanneer we motivatie manipuleren en 2) zien we effecten in de *keuzes* die mensen maken over het wel of niet uit willen voeren van cognitieve taken wanneer we motivatie manipuleren? Dat manipuleren van motivatie heb ik getracht te doen door middel van verschillende manieren om mensen te belonen en door middel van het toedienen van medicatie.

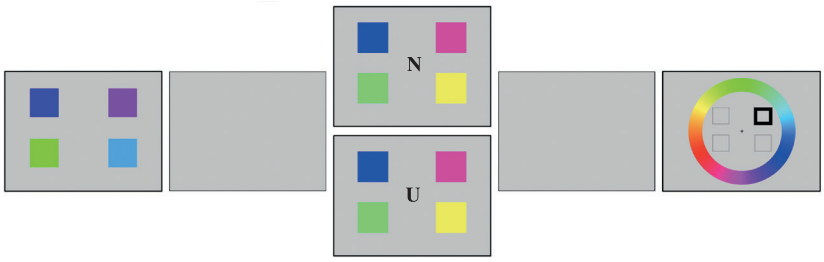
Dopamine

Het medicijn dat ik heb gebruikt is methylfenidaat, ook wel bekend onder de merknaam Ritalin®. Methylfenidaat verhoogt de hersenstof dopamine en mensen met ADHD, maar ook bijvoorbeeld studenten, gebruiken dit vaak om beter te kunnen presteren. Recente onderzoeken wijzen er echter op dat methylfenidaat niet alleen het vermogen maar ook de motivatie om cognitief te presteren kunnen beïnvloeden. Methylfenidaat is daarom bij uitstek geschikt om mijn onderzoeksvragen te beantwoorden.

Zoals gezegd kan beloning ervoor zorgen dat je beter presteert (of iets graag wilt doen), maar kan het er ook voor zorgen dat je het juist slechter gaat doen (of iets minder graag wilt doen). Een aantal eerdere onderzoeken benadrukt dat het wel eens zo zou kunnen zijn dat de effecten van beloning en van methylfenidaat afhangen van de hoeveelheid van de hersenstof dopamine die al in een diepgelegen gebied, het striatum genoemd, in je hersenen aanwezig is. Ik heb daarom in een aantal van mijn onderzoeken gemeten hoeveel dopamine mensen aanmaken in hun striatum door middel van een hersenscan (een PET scan).

Het experiment

Om de link tussen motivatie en cognitieve prestatie te onderzoeken heb ik veel gebruik gemaakt van een werkgeheugenspel dat onderzoeks-deelnemers speelden op de computer (zie Figuur 1). Deelnemers speelden een spel waarin ze elke beurt opnieuw een aantal vierkanten te zien kregen waarvan ze de kleuren moesten onthouden.



FIGUUR 1 | Het werkgeheugenspel

In het werkgeheugenspel krijgen deelnemers eerst een aantal vierkanten te zien waarvan ze de kleuren moeten onthouden. Later krijgen ze een tweede groep met gekleurde vierkanten te zien. Als de letter in het midden een "N" (negeer) is, moeten ze deze nieuwe vierkanten negeren en de kleuren van de oude vierkanten blijven onthouden. Als de letter in het midden een "U" (update) is moeten ze juist de nieuwe kleuren onthouden en de oude vergeten. Tenslotte moeten ze op een kleurenwiel aangeven welke kleur hoorde bij het omlijnde vierkant. In het geval ze de letter "N" hadden gezien is dat dus de kleur paars, maar in het geval ze de letter "U" hadden gezien is het de kleur roze.

Er waren twee verschillende versies die altijd hetzelfde begonnen: Deelnemers kregen kort een aantal vierkanten te zien waarvan ze de kleuren moesten onthouden, wat gevolgd werd door een grijs scherm. Daarna verschenen er, steeds op dezelfde plek als eerst, nieuwe vierkanten in nieuwe kleuren op het scherm. Afhankelijk van de letter die in het midden van het scherm stond moesten ze andere dingen doen met deze nieuwe kleuren. Als er de letter "N" (negeer) stond moesten ze deze nieuwe kleuren negeren en de oude kleuren blijven onthouden. Als er de letter "U" (update) stond moesten ze juist deze nieuwe kleuren onthouden en de oude kleuren vergeten. Dit werd opnieuw gevolgd door een grijs scherm waarna er een kleurenwiel op het scherm verscheen. Op de plek van een van de kleuren was de omlijning van een vierkant te zien en deelnemers moesten op het kleurenwiel aangeven welke kleur daarbij hoorde. Bijvoorbeeld, als er rechts boven een omlijning te zien was en er was aangegeven dat ze de nieuwe kleuren moesten negeren, dan moesten ze de kleur van het eerste vierkant rechtsboven aangeven. Als er was aangegeven dat ze moesten updaten en dus de nieuwe kleuren moesten onthouden, dan moesten ze de kleur van het tweede vierkant rechtsboven aangeven. Aangezien de kleuren maar erg kort op het scherm te zien waren (500 milliseconden) en het dus een grote mate van aandacht van de deelnemer vereiste, was dit een moeilijk spel. Door het gebruik van dit spel kon ik kijken naar de prestatie op taken die verschillende vormen van cognitieve vaardigheden testen: cognitieve stabiliteit (je focussen op informatie terwijl je nieuwe informatie moet negeren) en cognitieve flexibiliteit (het wisselen van je aandacht door nieuwe informatie juist binnen te laten).

Dit werkgeheugenspel heb ik gebruikt in vier van mijn vijf onderzoeken, gerapporteerd in de hoofdstukken 2 tot en 5 van dit proefschrift. In hoofdstuk 2 heb ik gekeken naar

hoe medicatie de keuze van deelnemers beïnvloedde tussen het moeten spelen van dit moeilijke spel of te doen waar ze zin in hadden. In de hoofdstukken 3 tot en met 5 heb ik gekeken naar hoe verschillende vormen van beloning de prestatie op de twee vormen van cognitieve vaardigheden beïnvloedde. Omdat er weinig tot geen effect van beloning leek te zijn op de prestatie op dit werkgeheugenspel, heb ik in hoofdstuk 6 een ander, al veel getest spel gebruikt om te kijken naar hoe beloning prestatie beïnvloedde. In de volgende sectie bespreek ik kort elk van de vijf onderzoeken en mijn bevindingen.

Methylfenidaat verhoogt motivatie voor cognitie vooral in mensen met veel dopamine in hun hersenen

Voor het onderzoek in hoofdstuk 2 moesten deelnemers een reeks keuzes maken tussen het spelen van het moeilijke werkgeheugenspel voor een bepaald geldbedrag of het mogen doen wat ze wilden voor een lager bedrag. Ze mochten dan bijvoorbeeld hun telefoon of de computer gebruiken voor een periode die gelijk was aan de tijd die het zou kosten om het spel te spelen. Deze reeks keuzes voeren ze eenmaal uit na het innemen van methylfenidaat en eenmaal na het innemen van een placebo pil. Op deze manier kon ik testen wat het effect was van methylfenidaat, dat dopamine verhoogt, op de motivatie van de deelnemers om het cognitief moeilijke spel te spelen. De resultaten wezen uit dat mensen een sterkere voorkeur hadden om het spel te spelen na het nemen van methylfenidaat dan na de placebo, maar dit effect was eigenlijk voornamelijk aanwezig in mensen met veel dopamine in hun striatum. Dus, om te weten wat methylfenidaat zal doen met je motivatie voor een cognitieve taak is het belangrijk om te weten hoeveel dopamine je al in je hersenen hebt.

Het is onduidelijk wat de effecten van beloning zijn op cognitieve prestatie

In de hoofdstukken 3 tot en met 5 heb ik gekeken naar de effecten van beloning op cognitieve stabiliteit (negeer) en flexibiliteit (update), gebruikmakende van het werkgeheugenspel. In hoofdstuk 3 beloofde (en gaf) ik deelnemers extra geld als ze het goed deden op het werkgeheugenspel. Hoeveel extra geld dat was verschilde per beurt. Ik zag echter geen verschil in prestatie tussen het beloven van veel of weinig geld. Ook was er geen verschil tussen het effect van beloning of stabiliteit of flexibiliteit. In hoofdstuk 4 heb ik daarom de beloningsregel aangepast, zodat mensen sowieso extra geld kregen, onafhankelijk van hoe goed ze het deden. Ik vond echter ook geen effect van deze vorm van beloning op prestatie of op stabiliteit versus flexibiliteit. Ik heb toen in hoofdstuk 5 weer gekeken naar beloning die afhankelijk is van je prestatie, zoals in hoofdstuk 3, maar nu vroeg ik deelnemers ook om een vragenlijst in te vullen

over hoe impulsief ze zijn, een eigenschap die waarschijnlijk gerelateerd is aan dopamine gehaltes in je hersenen. Opnieuw vond ik geen duidelijke effecten. Tenslotte heb ik in hoofdstuk 6 een ander, al veel getest spel gebruikt. Uit een eerder onderzoek was gebleken dat beloning ervoor zorgt dat deelnemers beter op dit spel werden als ze weinig dopamine in hun striatum hadden, maar dat ze slechter werden als ze veel dopamine in hun hersenen hadden. In hoofdstuk 6 heb ik deze bevindingen echter niet kunnen repliceren in een grotere groep deelnemers.

Conclusie

Samengevat heb ik in dit proefschrift op verschillende manieren getracht de relatie tussen motivatie en cognitie te beïnvloeden. In hoofdstuk 1 heb ik gevonden dat het dopamine verhogende middel methylfenidaat de motivatie om je cognitief in te spannen verhoogt, maar dat dit voornamelijk zo is als je al veel dopamine in een bepaald gebied van je hersenen, het striatum, hebt. Methylfenidaat werkt dus niet bij iedereen hetzelfde, wat belangrijk is om rekening mee te houden als je als student even een pilletje methylfenidaat (Ritalin®) wilt nemen voor een examen of wanneer je het als arts voorschrijft aan een patiënt.

Vervolgens heb ik in de hoofdstukken 3 tot en met 6 op verscheidene manieren getest of een financiële beloning een effect heeft op cognitieve prestatie, en belangrijker, of dat dit verschilt voor taken waarbij je een stabiele focus moet hebben en taken waarbij je juist steeds nieuwe informatie toe moet laten. Ik vond echter geen effecten van beloning. De open vraag is of dit ligt aan de specifieke taken die ik heb gebruikt of dat de effecten van beloning veel kleiner, of veel variabeler zijn dan we altijd gedacht hebben, wat grote gevolgen kan hebben voor bijvoorbeeld het onderwijs of de werkvloer.

Thank you notes

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About the author

Lieke Hofmans was born in 's-Hertogenbosch, the Netherlands on October 9th, 1991. After graduating from high school at d'Oultremontcollege Drunen in 2009 and a change of heart (or two) about which bachelor program to choose, she received a degree in Psychology from Tilburg University in 2013. Some extra courses taken at Radboud University Nijmegen and Chinese University of Hong Kong granted her access to the Neurasmus European master program in Neuroscience. This culminated in a diploma in Cellular and Molecular Biology – Specialization in Neurobiology from the University of Coimbra, Portugal, and a diploma in Medical Neurosciences from Charité Universitätsmedizin Berlin, Germany, in 2015. Having focused on immunotherapy to treat brain tumors for two years, she then thought it was time for a change. She felt prepared to embark the world of cognitive neuroscience as a PhD candidate in the Motivational and Cognitive Control lab headed by Roshan Cools at the Donders Institute in Nijmegen. It took quite some incomprehensible lab and center-wide meetings, in which all sorts of mysterious cognitive paradigms ("*which we are of course all familiar with*") were discussed, before she was convinced that she was in the right place. Several unsuccessful behavioral manipulations, coding frustrations and lunch breaks later, Lieke was able to put together a booklet describing her research projects and make it to the finish line.

Not being defeated by any setbacks, Lieke now happily continues as a postdoctoral researcher at the University of Amsterdam under the supervision of Wouter van den Bos, researching how social environment influences learning, cognition and decision-making in adolescents.

Aside from her research, she enjoys giving talks about (neuro)science to primary or high school classes and the occasional university student population.

Lieke rarely prepares a soup herself. She would rather buy one, or better yet, let it be delivered to her door.

List of publications

Hofmans, L., Westbrook, A., van den Bosch, R., Verkes, R.-J., Cools, R. (under review). Effects of average reward rate on vigor as a function of individual variation in striatal dopamine.

Westbrook, A., Ghosh, A., van den Bosch, R., Maatta, J.I., **Hofmans, L.**, Cools, R. (in press). Striatal dopamine synthesis capacity reflects smartphone social activity. *iScience*.

van Lieshout, L.L.F., van den Bosch, R., **Hofmans, L**., de Lange, F.P., Cools, R. Does dopamine synthesis capacity predict individual variation in curiosity? Preprint available at: https://www.biorxiv.org/content/10.1101/2020.10.13.337477v1

Hofmans, L., Papadopetraki, D., van den Bosch, R., Määttä, J.I., Froböse, M.I., Zandbelt, B.B., Westbrook, A., Verkes, R.-J. & Cools, R. (2020). Methylphenidate boosts choices of mental labor over leisure depending on striatal dopamine synthesis capacity. *Neuropsychopharmacology*, 45, 2170-2179. https://doi.org/10.1038/s41386-020-00834-1

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Westbrook, A., van den Bosch, R., Määttä, J.I., **Hofmans, L.**, Papadopetraki, D., Cools, R. & Frank, M.J. (2020). Dopamine promotes cognitive effort by biasing the benefits versus costs of cognitive work. *Science*, 367, 1362-1366. https://doi.org/10.1126/science.aaz5891

Cools, R., Froböse, M. I., Aarts, E. & **Hofmans, L.** (2019). Dopamine and the motivation of cognitive control. In M. D'Esposito & J.H. Grafman (Eds.), *The Frontal Lobes* (pp. 123-143). San Diego, CA: Elsevier BV. https://doi.org/10.1016/B978-0-12-804281-6.00007-0

PhD Portfolio

Name PhD candidate	Lieke Hofmans
Graduate School	Donders Institute for Brain Cognition and Behaviour
Department	Psychiatry, Radboudumc Donders Centre for Cognitive Neuroimaging, Radboud University
PhD period	May 2016 – May 2020
Promotors	Dr. Roshan Cools Dr. Robbert-Jan Verkes

Courses and workshops	Location	Year
Hands-on safety training non-invasive brain stimulation	Nijmegen	2016
Good Clinical Practice – WMO	Nijmegen	2016
Opfriscursus statistiek gedrags – en maatschappijwetenschappen	Nijmegen	2016
Toolkit: Essentials of major neuroimaging techniques	Nijmegen	2016
Radboud Leergang 'PhD in the Lead'	Nijmegen	2017
Nature masterclass 'Focus on Peer Review'	Nijmegen	2017
Advanced Math	Nijmegen	2017
Neuroimaging I	Nijmegen	2017
Neuroimaging II – Haemodynamic Methods	Nijmegen	2017
Bayesian Analysis with JASP: a fresh way to do statistics	Nijmegen	2017
BBSRC STARS – Advanced Methods for Reproducible Science	Windsor, UK	2017
SfN-FENS Summerschool Chemical Neuromodulation	Bertinoro, Italy	2017
Python for Social Scientists	Nijmegen	2018
Management voor Promovendi	Nijmegen	2018
Analytic Storytelling	Nijmegen	2018

Conferences	Location	Year
Donders Discussions	Nijmegen	2016
Donders Discussions	Nijmegen	2017
Symposium on the Biology of Decision-making	Paris, France	2018
Society for Neuroscience Meeting	San Diego, US	2018
Donders Discussions	Nijmegen	2019
Nederlandse Vereniging voor Psychonomie Winterconference	Egmond aan Zee	2019
Virtual Dopamine Conference	-	2020

Other activities	Location	Year
Supervision of bachelor and master students	Nijmegen	2016 – 2019
Workgroup teacher Brain and Cognition I	Nijmegen	2017
PhD representative Donders Centre for Cognitive Neuroimaging	Nijmegen	2017 – 2018
External Relations Donders Centre for Cognitive Neuroimaging	Nijmegen	2019
Invited Speaker 'Creative Cognition' at Bildung Academy	Amsterdam	2019
Radboud Science Team (onderzoekend leren in de klas)	Nijmegen	2019

Research data management

This research followed the applicable laws and ethical guidelines. Research Data Management was conducted according to the FAIR principles. The paragraphs below specify in detail how this was achieved.

Ethics

This thesis is based on the results of human studies, which were conducted in accordance with the principles of the Declaration of Helsinki. The medical and ethical review board Committee on Research Involving Human Subjects Region Arnhem Nijmegen, Nijmegen, the Netherlands has given approval to conduct these studies.

Findable, Accessible

The table below details where the data and research documentation for each chapter can be found on the Donders Repository (DR). All data archived as a Data Sharing Collection remain available for at least 10 years after termination of the studies (2020).

Chapter	DAC	RDC	DSC	DSC License
2	3017048.01_336		3017048.01_875 (overarching study) 3017048.01_346 (chapter 2)	RU-DI-HD-1.0 RU-DI-HD-1.0
3	3017048.02_366	3017048.02_120		
4	3017048.02_366	3017048.02_595		
5	3017048.03_079	3017048.03_395		
6	3017048.05_320		3017048.05_830	RU-DI-HD-1.0

DAC = Data Acquisition Collection, RDC = Research Documentation Collection, DSC = Data Sharing Collection

Informed consent was obtained on paper following the Centre procedure. The forms are archived in the central archive of the Centre for 10 years after termination of the studies.

Interoperable, Reusable

The raw data are stored in the DAC in their original form. For RDC and DSC long-lived file formats (e.g. .sav, .csv, .tif,) have been used ensuring that data remains usable in the future. The collections (DAC, RDC and DSC) are accompanied by readme files. Results are reproducible by the provision of descriptions of the experimental setup, raw data (DAC and DSC), analysis scripts or pipelines (RDC and DSC). Also, the used software including version numbers is specified.

Privacy

The privacy of the participants in this thesis has been warranted using random individual subject codes. A pseudonymization key linked this random code with the personal data. This pseudonymization key was stored on a network drive that was only accessible to members of the project who needed access to it because of their role within the project. The pseudonymization key was stored separately from the research data. The DSCs are shared under the restricted license RU-DI-HD-1.0, which provides extra statements for the protection of the identity of the participants.

Donders graduate school for cognitive neuroscience

For a successful research Institute, it is vital to train the next generation of young scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School for Cognitive Neuroscience (DGCN), which was officially recognised as a national graduate school in 2009. The Graduate School covers training at both Master's and PhD level and provides an excellent educational context fully aligned with the research programme of the Donders Institute. The school successfully attracts highly talented national and international students in biology, physics, psycholinguistics, psychology, behavioral science, medicine and related disciplines. Selective admission and assessment centers guarantee the enrolment of the best and most motivated students.

The DGCN tracks the career of PhD graduates carefully. More than 50% of PhD alumni show a continuation in academia with postdoc positions at top institutes worldwide, e.g. Stanford University, University of Oxford, University of Cambridge, UCL London, MPI Leipzig, Hanyang University in South Korea, NTNU Norway, University of Illinois, North Western University, Northeastern University in Boston, ETH Zürich, University of Vienna etc. Positions outside academia spread among the following sectors: specialists in a medical environment, mainly in genetics, geriatrics, psychiatry and neurology. Specialists in a psychological environment, e.g. as specialist in neuropsychology, psychological diagnostics or therapy. Positions in higher education as coordinators or lecturers. A smaller percentage enters business as research consultants, analysts or head of research and development. Fewer graduates stay in a research environment as lab coordinators, technical support or policy advisors. Upcoming possibilities are positions in the IT sector and management position in pharmaceutical industry. In general, the PhDs graduates almost invariably continue with high-quality positions that play an important role in our knowledge economy. For more information on the DGCN as well as past and upcoming defenses please visit: http://www.ru.nl/donders/graduate-school/phd/.

“Too much of anything is bad, but too much champagne is just right.”

– F. Scott Fitzgerald

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